Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation Reactions: Application Towards The Total Syntheses of Biologically Active Molecules

Theses submitted in accordance with the requirements of the University of Liverpool for the Doctor in Philosophy

By

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Abstract

The metal-catalysed allylic oxidation of alkenes has emerged as a powerful method for the functionalisation of sp^3 C-H bonds. This transformation has allowed for the expedient preparation of synthetically useful materials from hydrocarbon building blocks. With the development of air stable and environmentally benign copper(I)-NHC catalysts from readily available materials, it has been shown that these catalysts can participate in the allylic oxidation of alkenes in a effective manner. We have developed a powerful protocol for the functionalisation of alkenes into allylic alcohols and enones, by the use of different terminal oxidants in a divergent fashion. The highly regio- and chemoselective copper(I)-NHC-catalysed allylic oxidation has been examined in the syntheses of functionalised cyclopentenones and cyclohexenones, which has provided mechanistic insights into the oxidation. The system displays excellent tolerance of a plethora of sensitive functional groups and provides a general approach with high efficiency. It has been shown that high regioselectivity is not necessary straightforward and can depend on many factors, including stereoelectronic interactions. The studies towards the enantioselective variant *via* the desymmetrisation of the proposed prochiral intermediate utilising a range of chiral copper(I)-NHC catalysts was unsuccessful. The synthetic utility of this transformation has been validated by the total synthesis of (±)-untenone A in the shortest and most efficient approach to date. Studies towards the total synthesis of cephalimysin A are currently ongoing, which would employ the late stage copper(I)-NHC-catalysed allylic oxidation on a densely functionalised intermediate.

Dedication

I dedicate this to my family for all your support and financial help,

and I could not have done it without you.

Thank you and I love you all very much.

I hope I have done you all proud.

Acknowledgements

I would like to thank Professor P. Andrew Evans for the opportunity to work in the group and the guidance he has provided throughout my Ph.D. I have learnt a lot working alongside Andy, in which he has provided me with the ideal platform for a successful career in chemistry.

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Thanks to Gem for making the last two years a memorable and special period. We have done it. I love you very much.

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Chapter 1 **COPPER(I)-NHC-CATALYSED ALLYLIC OXIDATION OF ALKENES TO ALLYLIC ESTERS**

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List of Abbreviations

Å	angstrom
Ac	acetate
acac	acetylacetonato
AcOH	acetic acid
ad	adamantly
Ag	silver
APT	attached proton test
aq	aqueous
Ar	aryl
Au	gold
BDE	bond dissociation energy
BF_4	tetrafluoroborate

Bi	bismuth
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
^{t}BHP	*tert*-butyl hydroperoxide
Bn	Benzyl
BHT	butylated hydroxytoluene
Boc	*tert*-butoxycarbonyl
n-Bu	butyl
^{t}Bu	*tert*-butyl
Br	bromide
BORSM	based on recovered starting material
Bz	benzoate
BQ	benzoquinone
C	carbon
cap	caprolactamate
CCl_4	carbon tetrachloride
$CDCl_4$	deuterated chloroform
CF_3	trifluoromethane
CH_4	methane
CI	chemical ionisation
CO	carbon monoxide
Co	cobalt
Cl	chloride
Cu	copper
Cr	chromium
cat	catalytic
*m*CPBA	3-chloroperbenzoic acid

conv	conversion
Cy	cyclohexyl
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	*N*,*N*-diisopropyl azodicarboxylate
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMP	dimethylpyrazole
ds	diasteroselectivity
DIPEA	Diisopropylethylamine
2-EH	2-ethylhexanol
Et_2O	diethyl ether
EtOAc	ethyl acetate
ee	enantioselectivity
ESI	electrospray ionisation
eq	equivalent
eV	electron volt
Et	ethyl
EtCN	propionitrile
FCC	flash column chromatography
FTIR	fourier transform infrared
Fe	iron
g	gram
GC	gas chromatography

H	proton (hydrogen)
h	hour
H_2O	water
H_2O_2	hydrogen peroxide
Hg	mercury
HG-II	Hoveyda-Grubbs catalyst, second generation
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
Ir	iridium
IMes	1,3-*bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene
I	iodide
Imid	imidazole
IR	infrared
kcal	kilocalorie
K_2CO_3	potassium carbonate
KSE	kinetic solvent effect
LDA	lithium diisopropyl amine
$LiAlH_4$	lithium aluminium hydride
Ln	ligand set
M	molar

Me	methyl
mg	milligram
MHz	megahertz
mL	millilitre
mol	mol
Mo	molybdenum
mmol	millimole
Mg	magnesium
min	minute
Mn	manganese
MeCN	acetonitrile
MOM	methoxy methyl ether
MOMCl	chloromethyl methyl ether
MS	molecular sieves
N_2	nitrogen
NaCl	sodium chloride
$NaHCO_3$	sodium bicarbonate
Na_2CO_3	sodium carbonate
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
Ni	nickel
nm	nanometre
NMR	nuclear overhauser effect spectroscopy
NPhth	phthalimide
NO_2	nitro
O_2	molecular oxygen

oz	ounce
PA	picolinic acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pb	lead
Pd	palladium
PF_6	hexafluorophosphate
pka	acid dissociation constant
Ph	phenyl
$PhCF_3$	trifluoromethylbenzene
PhH	benzene
$PhIO_2$	iodosylbenzene
PhMe	toluene
PPh_3	triphenyl phosphine
Piv	pivaloyl
^{i}Pr	isopropyl
Pr	propyl
Pt	platinum
rt	room temperature
RCM	ring closing metathesis
Se	selenium
Sm	samarium
TBS	*tert*-butyl dimethylsilyl
TMS	trimethylsilyl
TBDPS	*tert*-butyl diphenyl silyl
TEP	Tolman electronic parameter

TFA	trifluoroacetyl
Tl	thallium
Ts	toluenesulfonyl
THF	tetrahydrofuran
TIPSCl	triisopropylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tf	trifluoromethanesulfonyl
TLC	thin layer chromatography
UV	ultraviolet
vs.	versus
Zn	zinc

Chapter 1

Copper(I)-NHC-Catalysed Allylic Oxidation of Alkenes to Allylic Esters

1.1. Introduction

1.1.1. Background and Significance

Carbon-oxygen bonds decorate countless pharmacologically important active agents. Hence, making the chemo-, regio- and stereoselective methods for the installation of this motif an indispensable tool in the armoury of organic chemists for both academic and industrial applications.[1] The ability to directly and selectively oxidise sp^3 C-H or sp^2 C=C bonds to furnish sp^3 C-O bonds in a mild and environmentally benign manner represents an important area of research. In this context, a number of transition metal-catalysed methods have been developed for the racemic and asymmetric synthesis of allylic alcohols and esters.[2] These methods often rely on expensive metals, ligands and often employ stoichiometric organometallic reagents, which are unsuitable for process development and industrial processes. Nonetheless, allylic oxidation has been employed for the construction of a plethora of natural products, pharmaceuticals and biological metabolites (Fig. 1.1).[3]

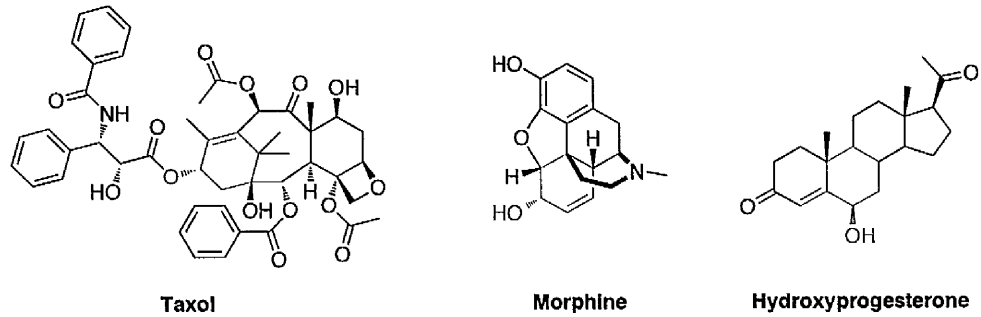
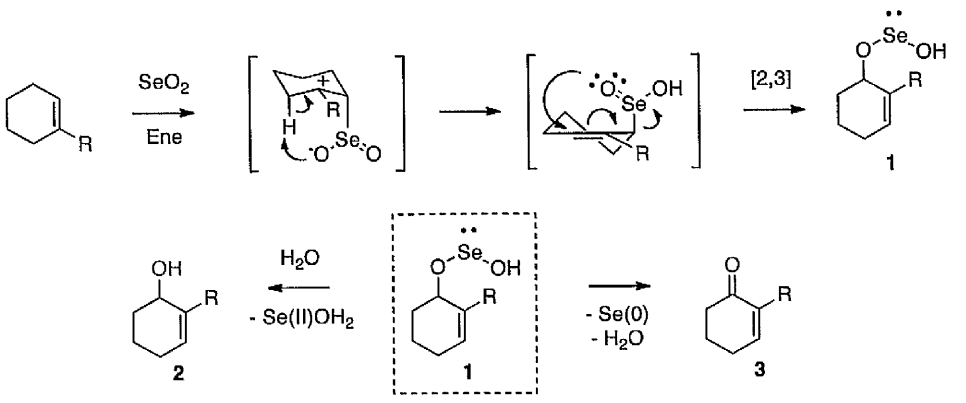


Figure 1.1 *Natural, Pharmaceutical and Biological Metabolite Products.*

1.1.2. Stoichiometric Selenium Allylic Oxidation

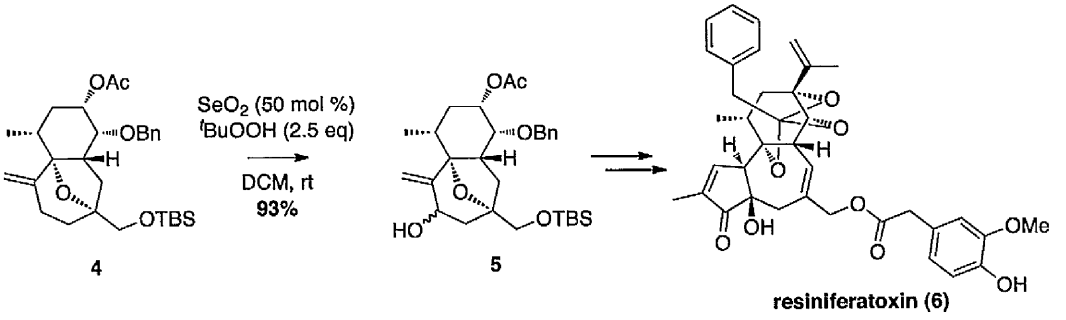
The first allylic oxidation reactions were carried out using selenium reagents as stoichiometric oxidants to afford the requisite allylic alcohols, which produces significant quantities of toxic by-products and waste making purification difficult and the disposal of the waste expensive. In 1932, Riley *et al.* discovered that selenium(IV) dioxide is an efficient reagent for the allylic oxidation of alkenes with excellent chemo- and regioselectivity.[4] Extensive progress has been made by several groups to establish the origin of the high degree of control through the examination of the mechanism of the oxidation.[5] Nonetheless, it was not until 1973, when Sharpless proposed that the reaction proceeds *via* an ene reaction followed by a [2,3]-sigmatropic rearrangement that a mechanism was established. This proposal was later supported by computational studies (Scheme 1.1).[6] For instance, the selenoxylic ester **1** can either furnish the allylic alcohol **2** or the α-β-unsaturated enone **3** by controlling the reaction conditions. These products are often formed in mixtures, which is in itself a limitation. This also explains why allylic oxidations utilising selenium(IV) always provide product where the oxidation has taken place at the most sterically congested allylic position, due to the two-step mechanism (Scheme 1.1).



Scheme 1.1 *Proposed Mechanism of Allylic Oxidation with Selenium(IV) Dioxide.*

1.1.3. Catalytic Selenium Allylic Oxidation

The stoichiometric selenium-mediated allylic oxidation reaction has been superseded by the catalytic version, also developed by Sharpless, using selenium dioxide in the presence of *tert*-butyl hydroperoxide.[7] The early versions of the catalytic selenium allylic oxidation reaction were performed using hydrogen peroxide, but these were relatively inefficient.[7] The mechanism for the catalytic transformation was presumed to proceed *via* the perselenious acid and the reoxidation of selenium(0)/selenium(II) to the redox active selenium(IV) state.[7] A benefit of using the selenium allylic oxidation reaction over current metal-catalysed methods, is that selenium dioxide reacts with a wide variety of alkenes, including exocyclic methylenes, which are generally inert to modern methods. For example, the treatment of the exocyclic alkene **4** with a sub-stoichiometric amount of selenium dioxide in the presence of *tert*-butyl hydroperoxide to afford the allylic alcohol **5** in 93% yield, which was a key intermediate in the total synthesis of resiniferatoxin **6** (Scheme 1.2).

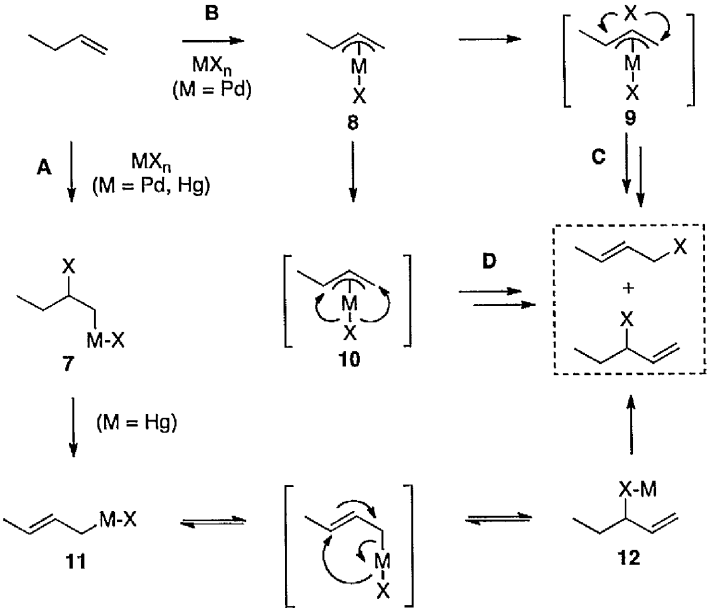


Scheme 1.2 *Selenium Allylic Oxidation in the Total Synthesis of Resiniferatoxin* ***6***.

1.1.4. Stoichiometric Metal-Acetate Allylic Oxidation

The construction of allylic esters utilising metal acetates $M(OAc)_n$ (generally M = Hg^{II}, Pd^{II}, Tl^{III}, Pb^{IV}) has proven to be a popular area of investigation. Nevertheless, there are significant drawbacks to these reagents, due to the toxicity of

the heavy metal.[8] These reagents generally provide good yields, albeit with poor regioselectivity for terminal alkenes which produce mixtures of the linear and branch allylic esters. The proposed mechanism for this oxidation reaction is similar to the aforementioned metal acetates, with the exception of mercury, which was proposed to proceed *via* a different pathway (Scheme 1.3).[9a,c] The palladium version is thought to occur *via* direct addition of PdX_2 to the alkene to generate **7** (Path **A**) or by the α-H-abstraction to furnish the π-allyl intermediate **8** (Path **B**). The palladium π-allyl intermediate **8** would then be subjected to nucleophilic attack, either by the external *trans* attack (Path **C**) *via* **9** or by the internal *cis* attack (Path **D**) *via* **10** to afford mixtures of the primary and secondary acetates.[10]

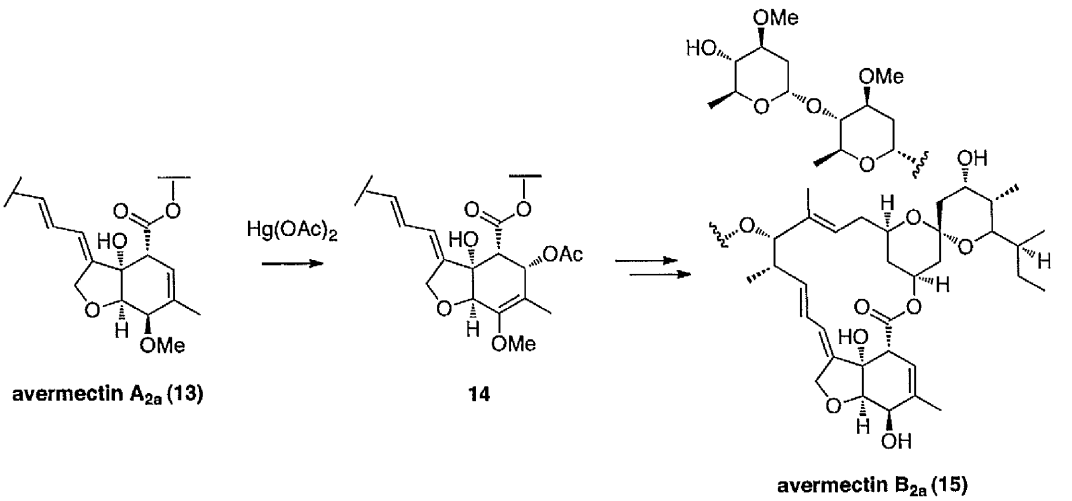


Scheme 1.3 *Proposed Mechanism for Palladium(II) and Mercury(II) Allylic Oxidation.*

Rappoport and coworkers proposed a variation on this mechanism in which a π-allyl mercury or ion pair intermediate was inconsistent with the product distribution.[9a,c] The formation of the allylic mercury acetate **11** from adduct **7**, led to the rearrangement of the primary mercuric acetate **11** to the secondary crotyl mercuric acetate **12**. The allylic ester isomerisation is presumably the result of the

non-Markovnikov acetoxymercuration, followed by deacetoxymercuration involving the original acetoxy group. Nonetheless, the resulting oxidation is not general or selective, affording a 40:60 mixture of the secondary and primary esters, respectively.[9a]

Mercury(II) acetate was used in the allylic oxidation of avermectin A_{2a} **13** in the total synthesis of avermectin B_{2a} **15** (Scheme 1.4). The oxidation of **13** gave the rearranged allylic acetate **14**, which after further derivatisation provided the demethylated avermectin B_{2a} **15**.[11]

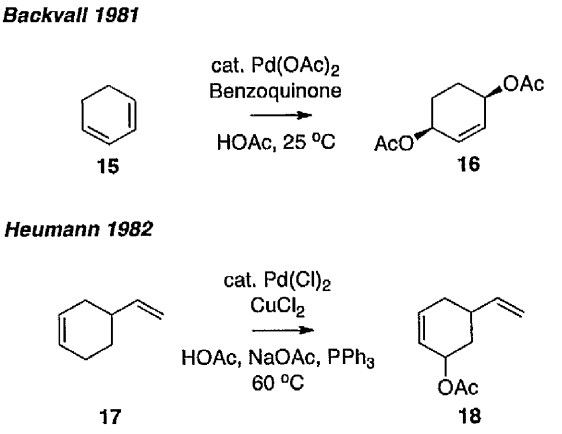


Scheme 1.4 *Mercury Acetate Allylic Oxidation in the Synthesis of Avermectin B_{2a} 15.*

1.1.5. Catalytic Palladium Allylic Oxidation

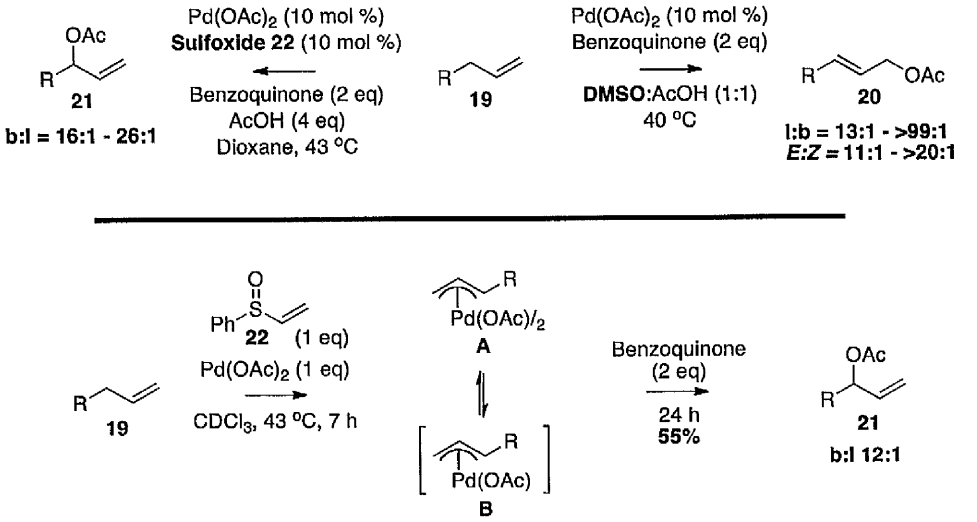
Catalytic palladium variants of the reaction have recently been developed, which is significantly less toxic than stoichiometric heavy metals. In 1982, Heumann *et al.* reported that catalytic quantities of palladium(II) chloride with copper(II) chloride as a reoxidant, provide the allylic acetate **18** in modest yield from the diene **17** (Scheme 1.5).[12] This reaction was improved by the same group utilising catalytic palladium(II) acetate with a *p*-benzoquinone/MnO_2 mixture as the reoxidant.[13] In 1981, Bäckvall and Nordberg reported a similar system for the allylic oxidation of the cyclohexadiene **15** to afford the *bis*-allylic acetate **16**.[14] The improvement in

efficiency was attributed to the reoxidation of palladium(0) to palladium(II) by the quinone, which also acted as a ligand for the palladium catalyst.[13,14]



Scheme 1.5 *Initial Catalytic Palladium(II) Allylic Oxidation.*

Recent developments into the palladium-catalysed allylic oxidation reaction have been focused on the terminal alkenes to solve the problem associated with regioselectivity in the formation of primary and secondary esters. In 2004, pioneering work by White and Chen demonstrated that the regioselectivity could be controlled *via* the catalyst (Scheme 1.6).[15]

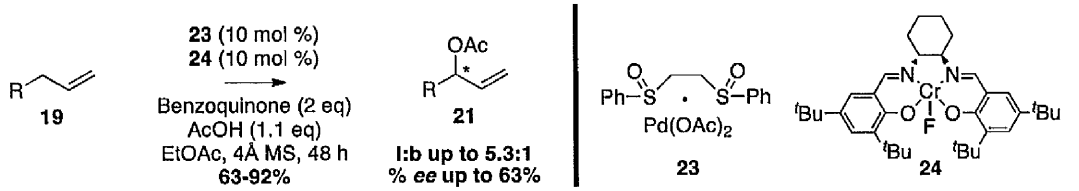


Scheme 1.6 *Palladium Catalyst Dichotomy and Mechanistic Insights.*

This demonstrated that linear allylic acetates **20** could be prepared from the terminal alkene **19** with excellent linear/branched and *E/Z* selectivity, using the palladium(II) acetate/benzoquinone system in the presence of DMSO. This

selectivity could be reversed by replacing DMSO with the sulfoxide **22**, which provided the branched allylic acetates **21** in equally impressive branched/linear ratios.[16] Additional studies have probed the origin of this selectivity by examining the active palladium species by ^{1}H-NMR. These studies indicated that the palladium dimer **A** was not observed by ^{1}H-NMR under catalytic conditions suggesting that it enters the catalytic cycle as the monomeric species **B**, because dimerisation is disfavoured at low concentration. They also proposed that the benzoquinone acts as the ligand in the functionalisation step, and that the active palladium/sulfoxide complex **22** aids the important initial C-H cleavage step.

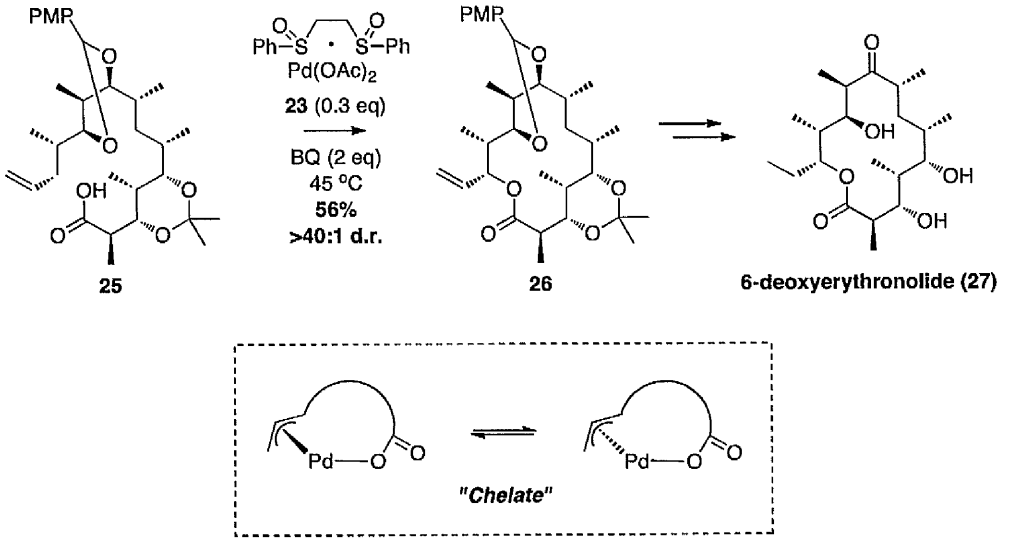
In 2008, White *et al.* reported an improved enantioselective allylic C-H oxidation using a chiral Lewis acid additive for terminal alkenes.[17] A mixture of palladium/sulfoxide catalyst **23** in the presence of a chiral chromium salen Lewis acid **24**, benzoquinone and acetic acid furnishes the enantiopure branched allylic acetate **21** (*b:l* up to 5.3:1) in excellent yield and enantioselectivity (up to 63% *ee*) (Scheme 1.7). This process currently provides the optimal method for the enantioselective allylic oxidation, which improved the previous method (36% *ee*) for terminal alkenes.[18]



Scheme 1.7 *Enantioselective Palladium(II) Allylic C-H Oxidation.*

Although the initial development of stoichiometric metal acetates, has led to modern palladium-catalysed methods, there are relatively few applications in total synthesis. White has recently applied the palladium-catalysed allylic oxidation to the latter stages of the total synthesis of 6-deoxyerythronolide B **27** (Scheme 1.8).[19] Treatment of the alkene **25** with the palladium catalyst **23** and benzoquinone,

provided the macrocycle **26** in 56% yield with excellent diasteroselectivity (Scheme 1.8). The stereochemical outcome was attributed to chelation of the palladium π-allyl with the carboxylic acid, which provides an intermediate with product-like transannular character.[19]

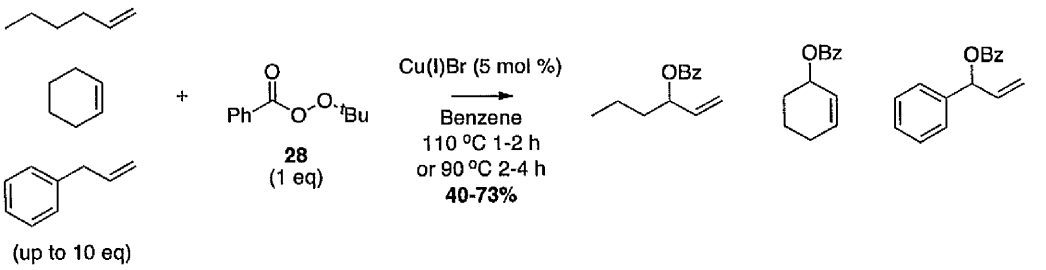


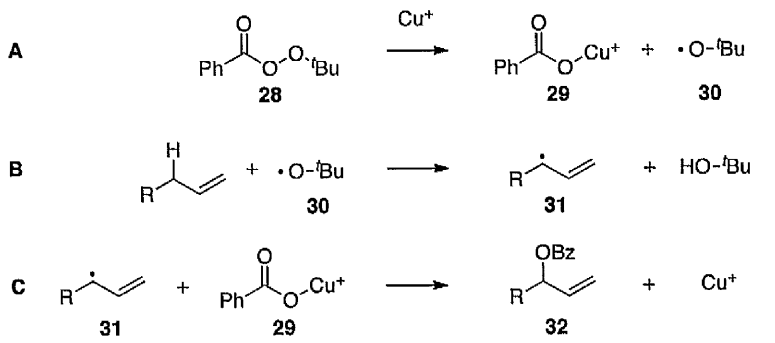
Scheme 1.8 *Intramolecular Palladium-Catalysed Allylic Oxidation Towards the Total Synthesis of 6-Deoxyerythronolide B 27.*

1.1.6. Catalytic Copper Allylic Oxidation

Many of the enantioselective allylic oxidation methods that preceded the palladium-catalysed version were accomplished using catalytic copper(I) salts and stoichiometric perester oxidants, a reaction which is known as the Kharasch-Sosnovsky reaction. For instance, Kharasch and Sosnovsky reported the catalytic copper(I) allylic oxidation of acyclic and cyclic alkenes with *tert*-butyl perbenzoate **28** in refluxing benzene provides the allylic benzoates in excellent yield and selectivity.[20] This process is optimal for terminal alkenes, from which only the secondary allylic benzoates were observed as products (Scheme 1.9).[20] In these reactions, an excess of the alkene was required (up to ten equivalents) making this oxidation somewhat limited in scope.

The mechanism proposed by Kharasch *et al.* is initiated with the homolytic cleavage of the perester oxygen-oxygen bond, to afford the copper(II)-carboxylate **29** and the *tert*-butoxy radical **30** (Scheme 1.9; **A**). The perester **28** is known to undergo thermal decomposition at 115 °C, thus path **A** can occur in the absence of metal salts.[20]





Scheme 1.9 *Initial Discovery and Proposed Mechanism for the Kharasch-Sosnovsky Reaction.*

The *tert*-butoxy radical **30** undergoes a regioselective hydrogen abstraction of the allylic hydrogen, to generate the allylic radical **31** and *tert*-butanol (Scheme 1.9, **B**). The alkyl radical **31** terminates with the copper(II)-carboxylate **29** to furnish the desired secondary allylic benzoate **32** and the regeneration of the copper catalyst (**C**). Kharasch noted that the absence of a primary allylic benzoate, contrasts a conventional free radical or carbocation intermediate, and that the allylic hydrogen displacement presumably occurs in a concerted manner. The propagation step **(B)** is chemoselective based on the bond dissociation energies of the C-H bond present, with weaker allylic/benzylic C-H bonds (<88 kcal/mol), undergoing selective hydrogen abstraction (Fig. 1.2).[21]

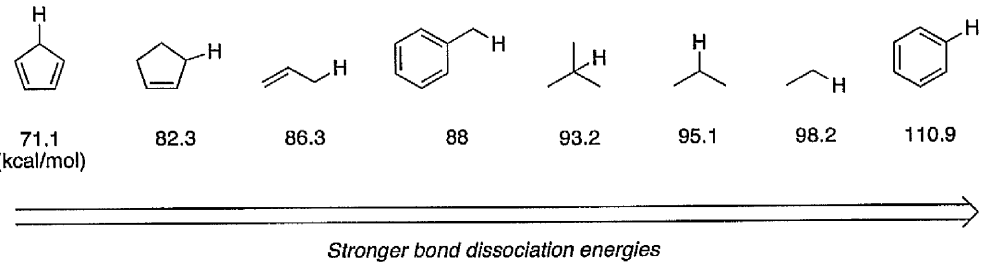
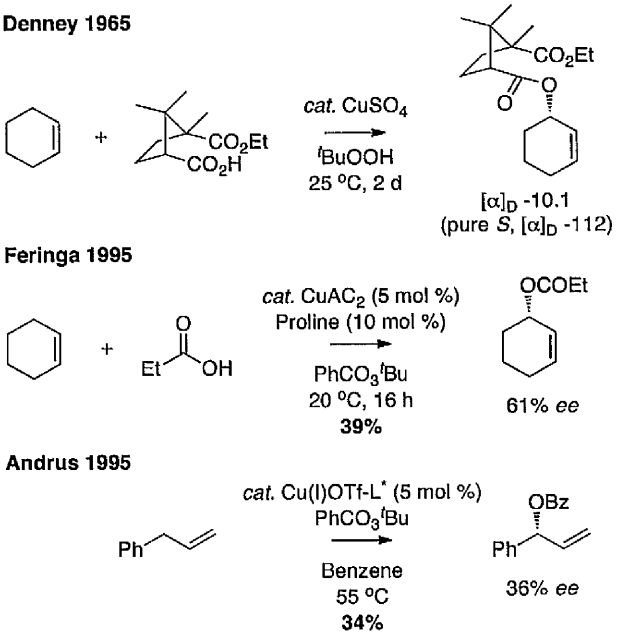


Figure 1.2 *Selected Bond Dissociation Energies (BDE's).*

Since Kharasch and Sosnovsky reported this reaction, many research groups have made significant advances in this area. Generally, reactions of acyclic alkenes are still underdeveloped, especially with asymmetric variants, whereas there are countless examples of the oxidation of simple cyclic alkenes. The majority of the asymmetric allylic oxidation reactions were implemented on cyclic alkenes, with Kharasch and Denney initially using chiral carboxylic acids, albeit with poor selectivity (Scheme 1.10).[22] Studies from several groups using a variety of chiral ligands and carboxylic acids provided oxidations, albeit with modest enantioselectivities. For instance, Feringa and coworkers described a proline-copper complex in the oxidation reaction, which provided up to 61% enantiomeric excess (Scheme 1.10).[23]



Scheme 1.10 *Early Enantioselective Kharasch-Sosnovsky Attempts.*

It was not until 1995, that Pfaltz and Andrus independently reported a major breakthrough in this area, using C_2-symmetric chiral copper(I)-bisoxazoline complexes to afford enantioenriched cyclic allylic esters with 65-84% enantiomeric excess.[18,24] Andrus proposed a model for the origin of the asymmetric induction, where a copper(III) intermediate adopts a distorted square planar geometry (Fig. 1.3). The allyl and benzoate groups are positioned either above or below the plane of the copper-bisoxazoline rings, which is dependent on the non-bonding interactions with the flanking *tert*-butyl groups on the bisoxazoline ligand.[18] The initial attack of the copper(II)-carboxylate on the allyl radical provides two diastereomeric adducts that lead to the respective enantiopure allylic acetates.

The copper(III) intermediate has also been supported from results obtained by Beckwith and Zavitsas, which demonstrated that the product can only originate from a copper (III) intermediate that proceeds through a pericyclic transition state.[25]

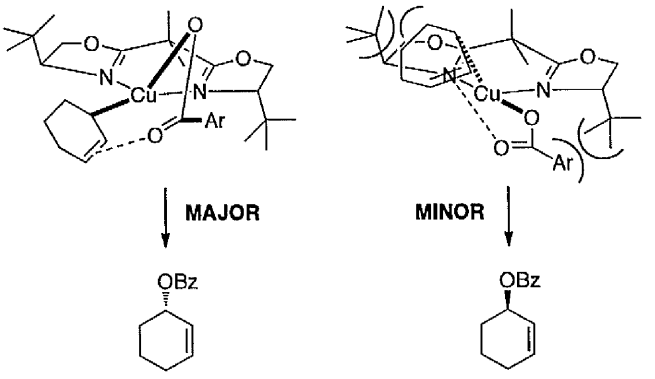
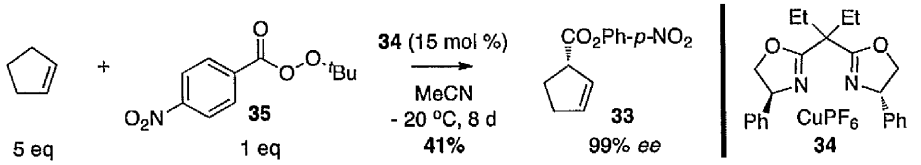


Figure 1.3 *Selectivity Model using Chiral Copper(I)-Bisoxazoline Complexes.*

In 2002, Andrus reported an optimised protocol that furnished the enantiopure allylic ester **33** in 99% enantiomeric excess from cyclopentene using the copper(I)-hexafluorophosphate-bisoxazoline complex **34** and *tert*-butyl *p*-nitroperbenzoate **35**. Nevertheless, the improved enantioselectivity was accompanied by diminished reactivity (Scheme 1.11).[26]



Scheme 1.11 *Highly Enantioselective Kharasch-Sosnovsky Reaction by Andrus et al.*

Furthermore, the reaction had limited scope, with only cyclic unsubstituted alkenes (cyclopentene, cyclohexene, cycloheptene and 1,5-cyclooctadiene) providing reasonable reactions and good enantiomeric excess.

In a related study, Katsuki *et al.* utilised this transformation for the oxidative desymmetrisation of racemic alkenes (Fig. 1.4).[27] The cycloalkene **36** undergoes hydrogen atom abstraction to furnish the *meso*-intermediate **37** *via* an allyl radical to generate the allylic ester **38**, bearing three stereogenic centres.

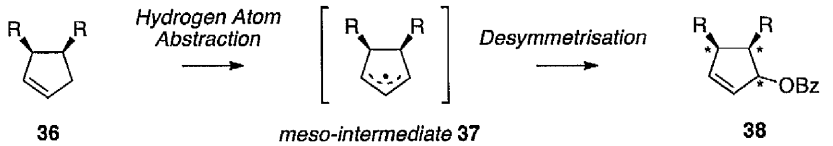
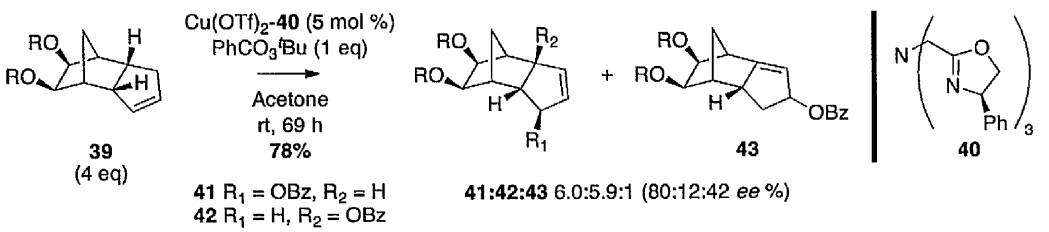


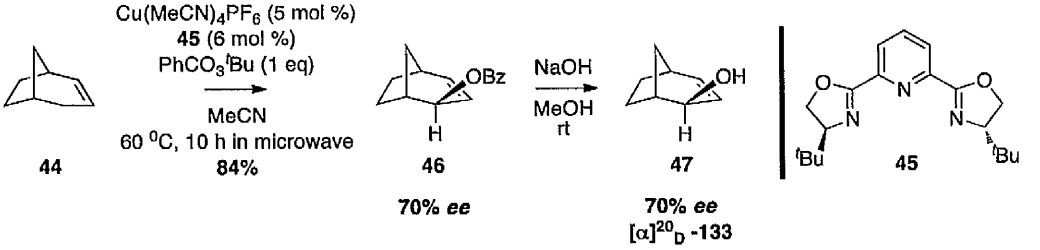
Figure 1.4 *Desymmetrisation of Racemic Alkene 36.*

The application of the desymmetrisation oxidation to other substrates provided variable results. Furthermore, treatment of the racemic oxygenated-dicyclopentenes **39** with the copper(II)-trioxazoline complex **40** provided the allylic benzoate esters **41**, **42** and **43** in 78% yield as a mixture of regio- and stereoisomers (Scheme 1.12). The poor selectivity was attributed to rapid and unselective trapping of the allylic radical. Nevertheless, the allylic benzoate ester **41** was obtained with good enantioselectivity (80% *ee*).



Scheme 1.12 *Oxidative Asymmetrisation of Racemic Alkenes 39 by Katsuki et al.*

In 2004, Clark *et al.* adapted the work done by Katsuki by developing the enantioselective allylic oxidation of the racemic bridged-bicyclic alkene **44** (Scheme 1.13).[28] The oxidation was achieved using the copper(I)-pybox complex **45** to afford the benzoate ester **46** in 84% yield and with 70% enantiomeric excess under microwave irradiation. Clark reported the isolation of a single regioisomer, wherein the oxidation occurred at the α-position of the bridgehead allylic position. Base hydrolysis of the allylic benzoate ester **46** provided the allylic alcohol **47** without erosion of the enantiomeric excess, which provided a compound of known absolute configuration.



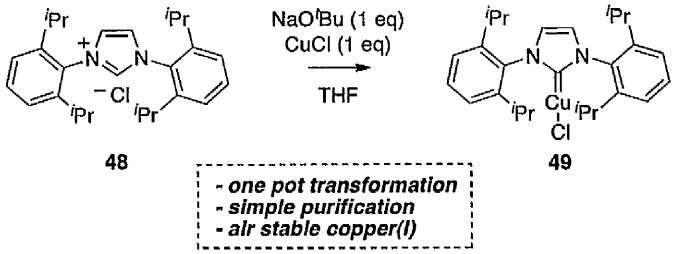
Scheme 1.13 *Enantioselective Symmetrising-Desymmetrising Allylic Oxidation by Clark et al.*

1.2. Copper(I)-NHC-Catalysed Allylic Oxidation of Cycloalkenes

1.2.1. Preliminary Results and Optimisation of Reaction Conditions

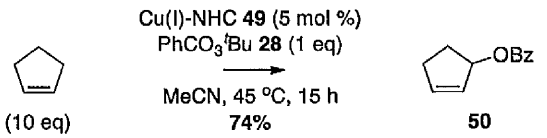
In 1991, Arduengo reported the stability and isolation of a crystalline *N*-heterocyclic carbene (NHC) with *N*-substituted adamantyl groups, to stabilise the carbene.[29] The *N*-heterocyclic carbenes are different from conventional carbenes, as they are electron rich and can form very strong σ-bonds with a majority of metals (often stronger than phosphines). At the time, there were a handful of metal-NHC complexes known, with the Grubbs second generation and Hoveyda-Grubbs second generation demonstrating the synthetic utility of these ligands after their initial discovery.[30] Copper(II) salts are generally air and moisture stable, whereas the

corresponding copper(I) salts are much less stable. The copper(I)-NHC catalyst **49** is readily available from the commercial imidazolium salt **48**, in the presence of base and copper(I) chloride (Scheme 1.14).[31] The copper(I)-NHC catalyst **49** is isolated as a pale yellow solid, which is stable in air.



Scheme 1.14 *Preparation of Copper(I)-NHC Chloride 23.*

We envisaged that the copper(I)-NHC catalysts would have comparable redox potential to the ligand-free copper(I) salts, albeit with enhanced stability making them suitable pre-catalysts for allylic oxidation, specifically the Kharasch-Sosnovsky reaction. Treatment of the perbenzoate **28** with excess cyclopentene in acetonitrile using a catalytic amount of **49** afforded the cyclopentenyl benzoate product **50** in 74% yield (Scheme 1.15).

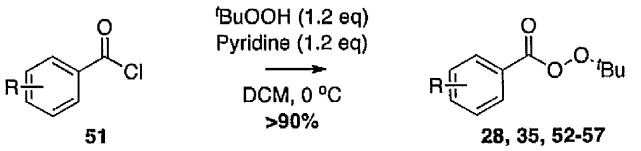


Scheme 1.15 *Initial Screen of Copper(I)-NHC 49 in the Kharasch-Sosnovsky Reaction.*

Hence, the copper(I)-NHC catalyst **49** is a more reactive catalyst than the original system. The improved reactivity is presumed to result from the increased electron density from the NHC ligand on the copper metal centre, which leads to the increased stability of the catalyst.

In order to improve the reactivity, a range of peresters with varying electronic and steric properties based on the Hammett equation were evaluated.[32] The peresters

were prepared from the commercially available acid chlorides **51** and *tert*-butyl hydroperoxide, and obtained as stable oils and solids (Scheme 1.16).[26]

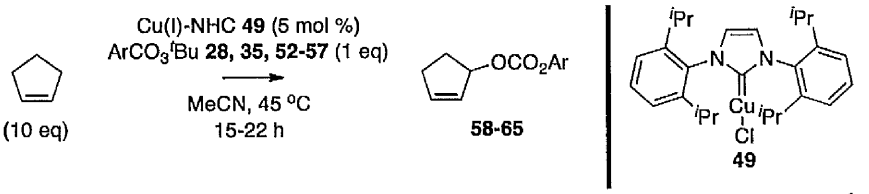


51 **28, 35, 52-57**

Scheme 1.16 *Preparation of Aryl-substituted Peresters.*

The individual peresters were then subjected to the Kharasch-Sosnovsky reaction using the copper(I)-NHC catalyst **49** under the standard reaction conditions to evaluate the effect on the rate of reaction and overall efficiency (Table 1.1).

Table 1.1 *Evaluation of Aryl-substituted Peresters.*[a]



Entry	Perester	Ar	σ	Product	Yield (%)[b]
1	**52**	*p*-OMe-Ph	-0.29	58	70
2	**53**	*p*-Me-Ph	-0.17	59	77
3	**28**	Ph	0	60	74
4	**54**	*p*-CF_3-Ph	0.54	61	83
5	***35***	***p*-NO_2-Ph**	***0.77***	***62***	***86***
6	**55**	*o*-Cl-Ph	-	63	73
7	**56**	*o*-NO_2-Ph	-	64	58
8	**57**	*o*-OMe-Ph	-	65	56

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields.

Table 1.1 summarises the results of this study in which the *tert*-butyl 4-nitrobenzoperoxoate **35** proved optimal with respect to the efficiency (Table 1.1, entry 5). In general, all the modified peresters were successful oxidants in the reaction with the electron poor examples providing optimal efficiency (entries 4 and 5). The *ortho*-substituted peresters **55-57**, which are sterically and electronically

biased, provided reduced reactivity, for example 22 hours *vs.* 15 hours and reduced efficiency (entries 6-8). The *ortho* groups can potentially interfere in the formation of the copper(II)-carboxylate and/or in the recombination of the copper(II)-carboxylate with the alkyl radical (Scheme 1.5, **A** and **C**). Additional optimisation studies focused on the examination of different copper(I)-NHC catalysts (Fig. 1.5).

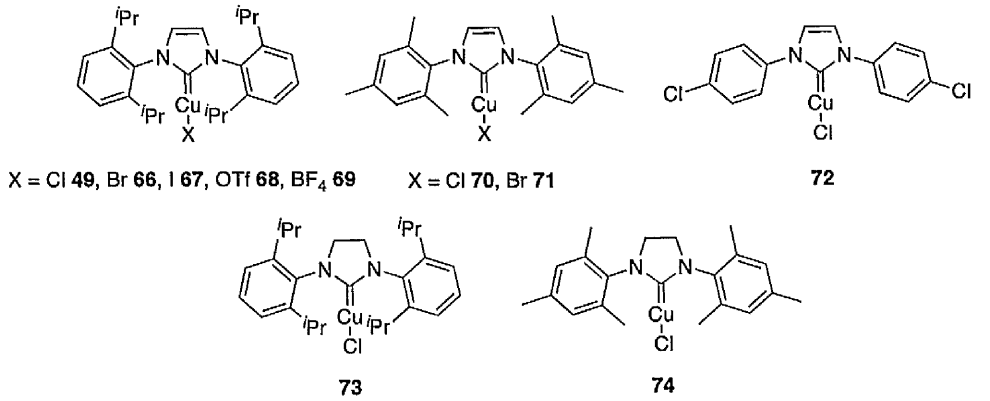
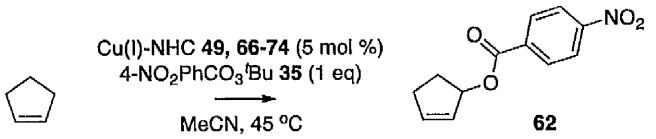


Figure 1.5 *Prepared Copper(I)-NHC Catalysts.*

Table 1.2 outlines the summary of this study, which provided some interesting trends, with regard to the catalyst counterion. For example, the chloride **49** and bromide **66** are excellent pre-catalysts, whereas the iodide **67** was very poor (Table 1.2, entries 1-3). Additionally, outer-sphere counter ions (OTf and BF_4) also led to reduced efficiencies (entries 4 and 5). Reducing the steric bias of the pre-catalyst **70** furnished the ester **62** in 81% yield with an increased relative rate of reaction (entry 6). Adjusting the catalyst loading was unsuccessful and the corresponding bromide **71**, gave comparable results to the bromide **66** (entries 7-9). The difference between IMes and IPr is presumably due to the steric environment around the metal centre. Interestingly, the electronic nature of the NHC did not seem to affect the oxidation, since the electron deficient *para*-chloro **72**, electron rich **73** and **74**, afford the ester **62** in comparable yields over a similar time period (entries 10-12).

Table 1.2 *Evaluation of Copper(I)-NHC Catalysts.*[a]



Entry	Cu(I)-NHC	Time	Yield (%)[b]
1	**49**	15	86
2	**66**	22	78
3	**67**	48	24
4	**68**	48	41
5	**69**	48	43
6	***70***	***6***	***81***
7	**70** (1 mol %)	18	45
8	**70** (20 mol %)	2	14
9	**71**	15	77
10	**72**	15	75
11	**73**	15	75
12	**74**	15	84

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields.

Hence, this study indicates that the steric component of the NHC is much more important than the electronic component. A comparison of the electronics of the IPr and IMes NHC ligands indicate they are negligible (e.g. 2051.5 and 2050.7 TEP, respectively).[33] Whereas, the steric hindrance is quite significant for these ligands (e.g. 47.6% and 36.3% using $\%V_{bur}$, respectively) (Fig. 1.6).[34]

The study illustrated that more electronegative counter ions (Cl = 3.16, Br = 2.96, I = 2.66)[35] are detrimental to the reaction, but size could also play a part here as large counter ions could interfere with the radical recombination process (Cl = 0.181 nm, Br = 0.196 nm, I = 0.220 nm).[36]

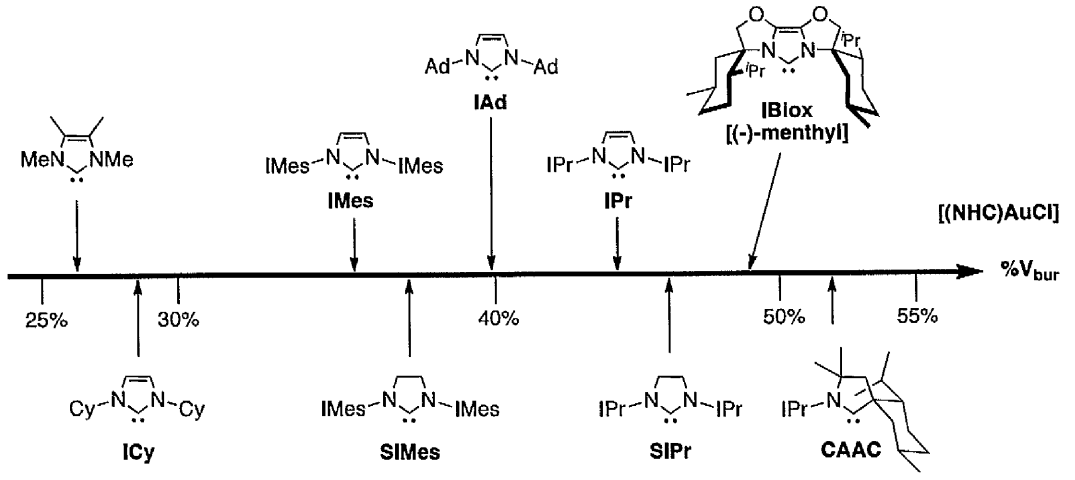
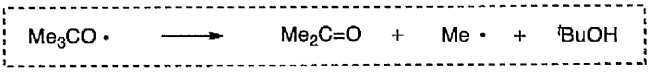


Figure 1.6 *Comparison of %V_{bur} for known [(NHC)AuCl] Complexes.*

We sought to examine alternative solvents since the kinetic solvent effect (KSE) play a minor role in free radical reactions and solvents such as benzene, ethanol, carbon tetrachloride and even water are used due to their compatability with free radicals. Moreover, the hydrogen abstraction from a C-H bond by an alkoxy radical does not suffer from KSE, in contrast to the three other possible unimolecular alkoxy radical destroying reactions.[38] Polar and hydrogen bonding donor solvents are known to promote the competition between hydrogen abstraction and β-scission of the *tert*-butoxy radical, hence it was important to investigate the effect of the solvent on the oxidation reaction (Scheme 1.17).[39]



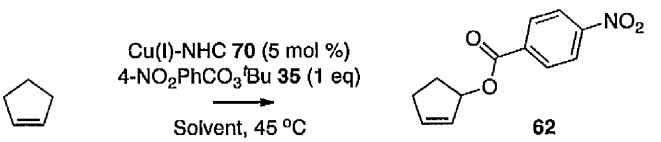
Solvent	*tert*-Butanol/Acetone
Benzene	3.5
Acetonitrile	1.6
Acetic acid	1.1

Scheme 1.17 *Kinetic Solvent Effect in β-scission.*

Table 1.3 summarises the results for this study. The catalyst **70** was only sparingly soluble in benzene, ethyl acetate and ethanol, making the reaction heterogeneous, which led to extended reaction times and moderate yields (entries 1, 2 and 5). Alternatively, the catalyst is completely soluble in dichloromethane,

acetone and nitromethane, albeit they were detrimental to the oxidation (entries 3, 4 and 6 *vs.* 7). Acetonitrile provided the optimal solvent with full conversion after 6 hours in 81% yield, which was improved at higher concentration to 87% yield (entry 7 *vs.* 9).

Table 1.3 *Evaluation of Solvents.*[a]



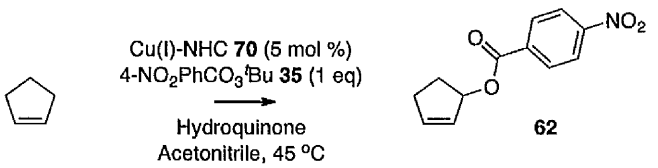
Entry	Solvent (0.125 M)	εr(ω)	Time (h)	Yield (%)[b]
1	Benzene	2.3	48	43
2	Ethyl acetate	6.0	48	43
3	Dichloromethane	9.1	18	52
4	Acetone	21	22	67
5	Ethanol	24	144	7
6	Nitromethane	36	36	60
7	Acetonitrile	37	6	81
8	Acetonitrile (0.25 M)	37	6	82
9	***Acetonitrile (1 M)***	***37***	***6***	***87***

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields.

Interesting, the use of nitromethane afforded 60% yield, even though the BDE of the nitromethane C-H bond is ~103 kcal/mol, compared to the C-N bond of ~60 kcal/mol (Table 1.6, entry 6).[40] We envision that the weaker C-N bond undergoes more facile homolytic cleavage under these conditions. This observation could provide an alternative mechanism alongside the one proposed tentatively by Kharasch, involving a possible carbon centred radical formed from the β-scission, for hydrogen abstraction.

In order to eliminate the possibility of a non-radical pathway for the copper(I)-NHC-catalysed allylic oxidation, a radical scavenger (hydroquinone) was added in varying amounts using the optimised reaction conditions (Table 1.4).

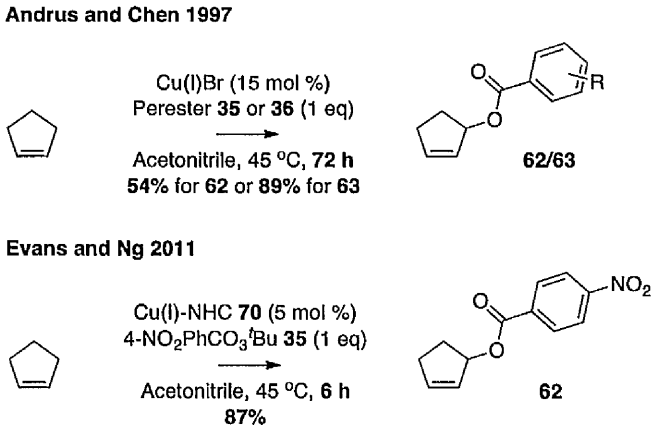
Table 1.4 *Radical Scavenger Experiment.*[a]



Entry	Hydroquinone (eq)	Yield (%)[b]
1	0.05	76
2	0.5	trace
3	1	-

[a]**Reactions were performed on 0.25 mmol scale.**
[b]**Isolated yields.**

In the presence of a catalytic amount of the radical scavenger, hydroquinone, the reaction still proceeds in excellent yield (Table 1.4, entry 1). However, the analogous process performed in the presence of half or a full equivalent of hydroquinone results in the inhibition the oxidation reaction (entries 2 and 3). Uemura has suggested an ionic pathway for the rhodium(II) acetate allylic oxidation reaction, which was also inhibited by hydroquinone.[41]



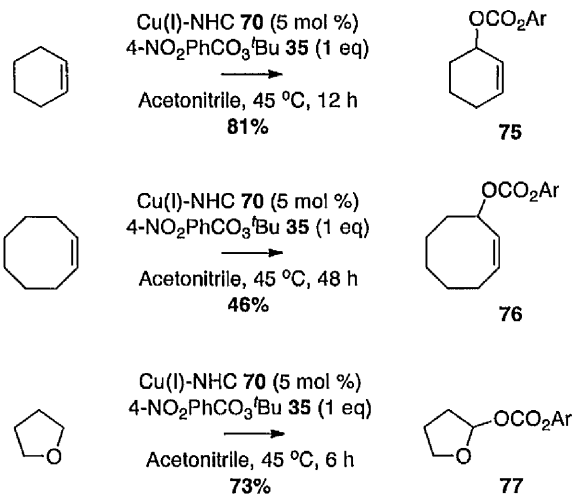
Scheme 1.18 *Comparison of the Optimal Copper(I) Bromide vs. Copper(I)-NHC Catalyst.*

The utility of copper(I)-NHC catalysts is evident upon comparison to the achiral Kharasch-Sosnovsky reaction reported by Andrus and Chen. For instance, the ester **62** was obtained in 54% yield with 15 mol % copper(I) bromide in 72 hours,

whereas the copper(I)-NHC catalyst **70** provides ester **62** in 87% yield, with 5 mol % catalyst loading and 12-fold increase in reaction rate (Scheme 1.18).[42] Nevertheless, the former method provides the ester **63** in an improved 89% yield using the *tert*-butyl 2-chlorobenzoperoxoate **55** (Table 1.1, entry 6).

1.2.2. Scope and Limitations

The scope of the copper(I)-NHC-catalysed allylic oxidation reaction was investigated with a variety of cyclic and acyclic alkenes to examine the scope of the system (Scheme 1.19). Cyclohexene and cyclooctene are oxidised to furnish the allylic esters **75** and **76** in 81% and 46% yield, respectively under the standard conditions, whereas cyclooctene required a prolonged reaction time (12 hours *vs.* 48 hours). Finally, the process was examined on heteroatom derivatives. Treatment of tetrahydrofuran under the optimised conditions afforded the tetrahydrofuran-2-yl ester **77** in 73% yield.



Scheme 1.19 *Scope of Copper(I)-NHC-Catalysed Allylic Oxidation.*

Although the copper(I)-NHC-catalysed conditions proved to be superior for the oxidation of five- and six-membered cycloalkenes, including tetrahydrofuran, they are sub-optimal for substrates containing larger rings and for acyclic alkenes.

1.2.3. Investigation into the Enantioselective Copper(I)-NHC-Catalysed Allylic Oxidation

Having established the Kharasch-Sosnovsky oxidation reaction using copper(I)-NHC catalysts, the enantioselective version was examined. Although, reactions promoted by copper-bisoxazoline complexes proceed with excellent enantiomeric excess, there are limitations. A particularly attractive feature of *N*-heterocyclic carbenes as ligands is that the stereoelectronics can be tuned in a modular manner, making it an attractive scaffold for asymmetric reactions.[43] Hence, a variety of chiral copper(I)-NHC complexes can be readily prepared from commercially available enantiopure amines (Fig. 1.7).

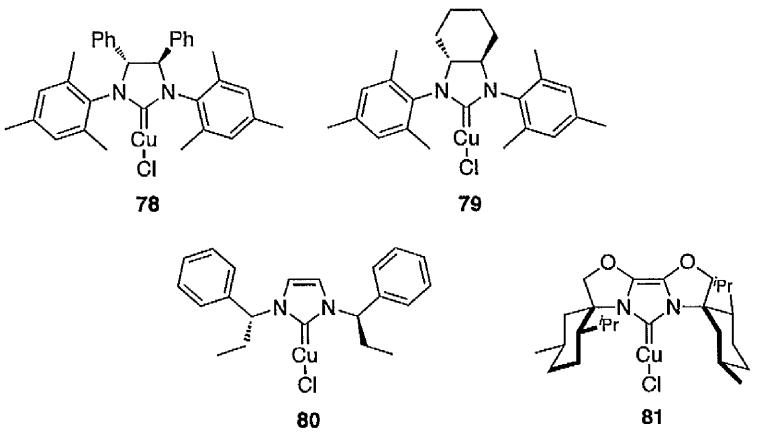
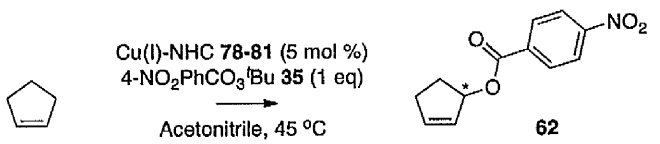


Fig 1.7 *Prepared Chiral Copper(I)-NHC Catalysts.*

Table 1.5 outlines the outcome of the oxidation reactions using the chiral copper(I)-NHC catalysts. Although the copper(I)-NHC complexes **78-81** were efficient catalysts for allylic oxidation, producing the allylic ester **62** in 75-79% yield, the products were racemic (Table 1.5, entries 1-4). The IBiox[(-)-menthyl] NHC ligand **81** developed by Glorius *et al.*, was especially disappointing, since it is one of the most sterically demanding NHC ligands known, based on the buried volume (50.4% compared to 36.3% for the IMes ligand).[45] The results indicate that there is a fundamental difference between the complexes containing chiral NHC ligands and copper(I)-bisoxazoline complexes. This is presumably the result of the

linear conformation of the copper(I)-complex placing the steric environment distal to the chiral environment in the enantiodetermining step.[44]

Table 1.5 *Evaluation of Chiral Copper(I)-NHC Catalysts.*[a]



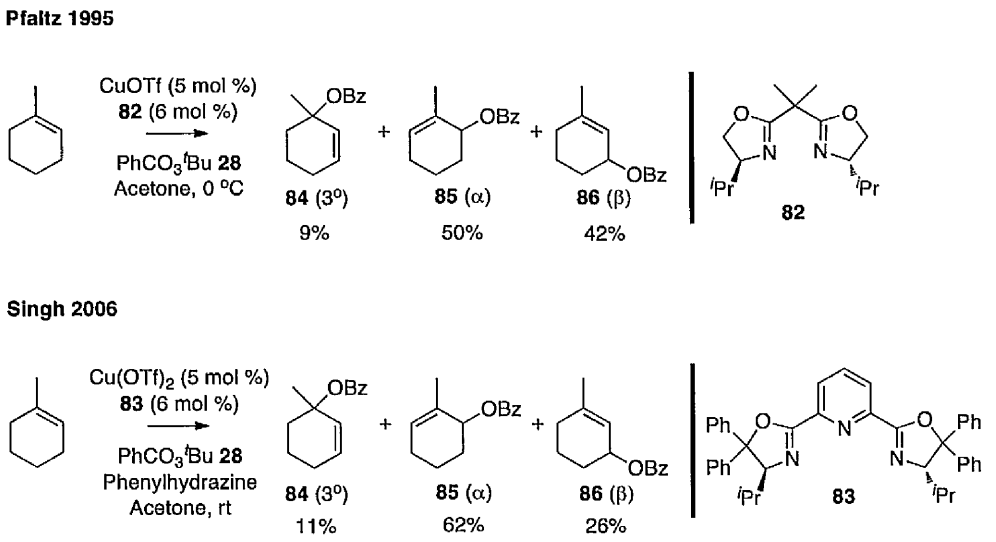
Entry	Cu(I)-NHC	Yield (%)[b]	*ee* (%)[c]
1	**78**	79	0
2	**79**	75	0
3	**80**	76	0
4	**81**	75	0

[a]**Reactions were performed on 0.25 mmol scale.** [b]**Isolated yields.** [c]**By HPLC.**

1.3. Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of Cycloalkenes

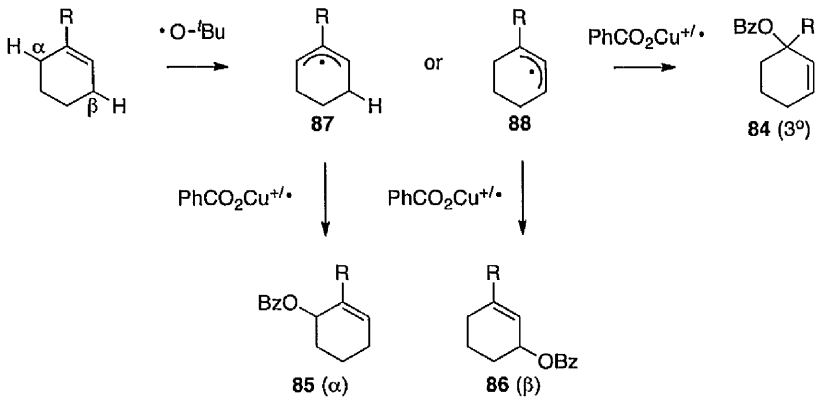
1.3.1 Introduction and Background

The Kharasch-Sosnovsky reaction is an effective method for the allylic oxidation of alkenes, but has been largely limited to simple substrates, namely unsubstituted alkenes due to problems with regiocontrol in unsymmetrical derivatives. For instance, the oxidation of 1-methylcyclohexene with perester **28** using the copper complex of the chiral ligand **82** furnished a mixture of the allylic benzoates **84/85/86** in quantitative yield favouring **85**:**86** (1:1).[46] Whereas, the oxidation using the copper complex of the chiral ligand **83** favoured **85** in 62% yield. Scheme 1.21 outlines the origin of the poor selectivity, in which the initial abstraction can occur at two potential allylic hydrogen sites: α to the R group to generate the allyl radical **87** and β to the R group to furnish the allyl radical **88**. The allyl radical **87** terminates with the copper carboxylate to afford the α-benzoate ester **85**, whilst the allyl intermediate **88** terminates to furnish the tertiary benzoate ester **84** or the β-benzoate ester **86** (Scheme 1.21).



Scheme 1.20 *Regioselectivity Issues with 1-Methylcyclohexene.*

These observations are consistent with the experimental results and the fact that a bulky ligand is likely to reduce the amount of the tertiary allylic benzoate ester **84**. It is also conceivable that the allylic hydrogen abstraction would generate the allyl radical **88** over radical radical **87**.



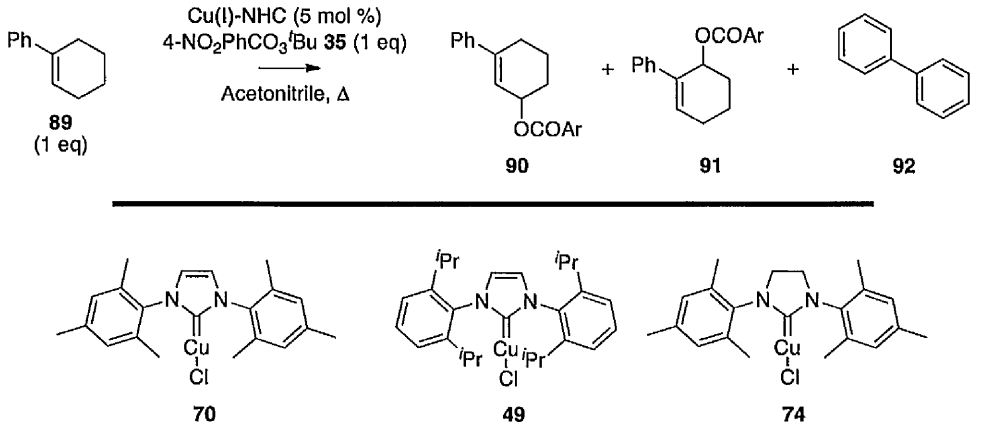
Scheme 1.21 *Proposed Regiomeric Outcome of Pfaltz and Singh's Work.*

1.3.2. Preliminary Results, Optimisation of Reaction Conditions and Mechanistic Insights

The allylic oxidation of 1-phenylcyclohexene **89** was examined using the *tert*-butyl 4-nitrobenzoperoxoate **35** and a range of copper(I)-NHC catalysts as outlined in Table 1.6.

Treatment of **89** (1 equivalent) with the copper(I)-NHC catalyst **70** under the standard conditions furnished the allylic esters **90** and **91** in 20% yield, albeit with good regioselectivity (10:1) (Table 1.6, entry 1). Interestingly, the β-allylic ester **90** was isolated as the major product, which contrasts results obtained by Pfaltz and Singh using their respective oxidation conditions.[46]

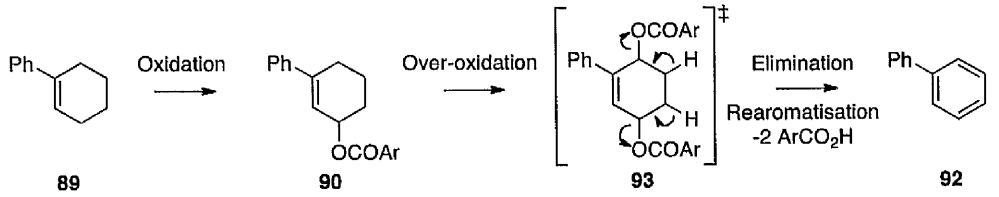
Table 1.6 *Preliminary Allylic Oxidation of 1-Phenylcyclohexene* ***89***.[a]



Entry	Cu(I)-NHC	Temp. (°C)	Yield 90+91 (%)[b]	90:91[c]
1	**70**	45	20	10:1
2	**70**	60	21	5:1
3	***49***	***45***	***25***	***≥19:1***
4	**74**	45	21	10:1

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields. [c]Determined by ^{1}H-NMR on crude mixtures.

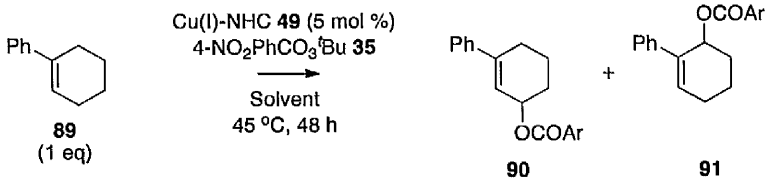
Although the oxidation with IPr **49** and SIMes **74** catalysts produced excellent regioselectivity (up to 19:1), the yields are poor (entries 3 and 4). Low yields were attributed to the formation of biphenyl **92** as a major byproduct. The biaryl **92** is presumably derived from the over-oxidation of the mono-allylic ester **90** to furnish the *bis*-allylic ester **93** and subsequent double elimination (Scheme 1.22).



Scheme 1.22 *Proposed Formation of Biphenyl Side-Product* ***92****.*

The unusual selectivity prompted further investigation using the substituted cyclohexene **89**. Table 1.7 outlines the results from the examination of the effect of solvent in reactions promoted by the copper(I)-NHC catalyst **49**. Increasing the *tert*-butyl 4-nitrobenzoperoxoate **35** results in a modest increase in yield, albeit with lower regioselectivity (Table 1.7, entry 1). Dimethylsulfoxide and dichloromethane were ineffective (entries 2 and 3), whereas, when the *tert*-butyl 4-nitrobenzoperoxoate **35** was utilised as the limiting reagent, a similar yield and regioselectivity were obtained (entry 4 *vs.* entry 1). This observation is important because, ideally for widespread application, the alkene would generally be the limiting species. Unfortunately, the *tert*-butyl 4-nitrobenzoperoxoate **35** provides poor yields and regioselectivity with the copper(I)-NHC catalysts due to the further oxidation of **90** (*vide supra*).

Table 1.7 *Evaluation of Solvents using Copper(I)-NHC Catalyst* ***49****.*[a]



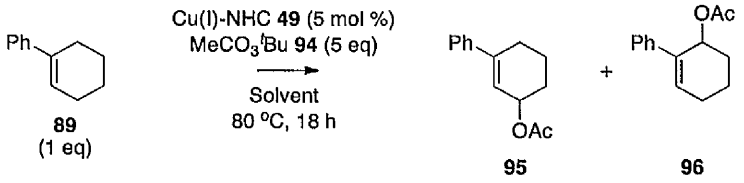
Entry	Solvent	35 (eq)	Yield 90+91 (%)[b]	90:93[c]
1	Acetonitrile	1.5	38	4:1
2	Dimethylsulfoxide	1.5	28	7:1
3	Dichloromethane	1.5	29	5:1
4[d]	Acetonitrile	1	34	4:1

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields. [c]Determined by ^{1}H-NMR on crude mixtures. [d]5 eq of alkene used.

In light of this limitation, an alternative strategy for the allylic oxidation of **89** was examined. The *tert*-butyl peracetate is cheap and commercially available, which avoids the *de novo* synthesis of the perester. Moreover, the generated allylic acetate (acetic acid, pKa = 4.76) is a poorer leaving group to the corresponding allylic *p*-nitrobenzoate (*p*-nitrobenzoic acid, pKa = 3.41), which was expected to avoid the over-oxidation/elimination pathway.[47]

Table 1.8 highlights the allylic oxidation of 1-phenylcyclohexene **89** with the copper(I)-NHC catalyst **49** and the *tert*-butyl peracetate **94** in a range of solvents. Although the reactions proceed in modest yields, acetonitrile and benzene provided optimal regioselectivity (≥19:1).

Table 1.8 *Evaluation of Solvents using tert-Butyl Peracetate* ***94.***[a]



Entry	Solvent	Yield 95+96 (%)[b]	95:96[c]
1	Acetonitrile	34	19:1
2	Dichloroethane	30	8:1
3	*tert*-Butanol	41	8:1
4	Toluene	46	12:1
5	Ethyl acetate	24	11:1
6	***Benzene***	***42***	***19:1***

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields. [c]Determined by ^{1}H-NMR on crude mixtures.

Table 1.9 outlines further optimisation, which involved varying the alkene/perester stoichiometry and the copper(I)-NHC catalyst loading. Treatment of excess **89** with the perester as the limiting reagent furnished an improved yield of **95/96**, albeit with poor regioselectivity (Table 1.9, entries 1-3). Alternatively, using excess perester afforded a modest result (entry 4). Unfortunately, the regioselectivity decreased as the perester stoichiometry increased (entries 4-6). The optimal results

were obtained using toluene and 10 equivalents of the perester with 10 mol % copper(I)-NHC catalyst **66** (entry 9). This furnished the allylic acetates **95/96** in 70% yield with ≥19:1 regioselectivity, favouring **95**. The allylic oxidation reaction in toluene is unusual, as there was low conversion during the first 24 hours, but enhanced rates over the next 24 hour period. The explanation for this phenomenon is not obvious, but it was proposed that the catalyst is altered over the course of the oxidation reaction thus producing a more reactive catalytic species.

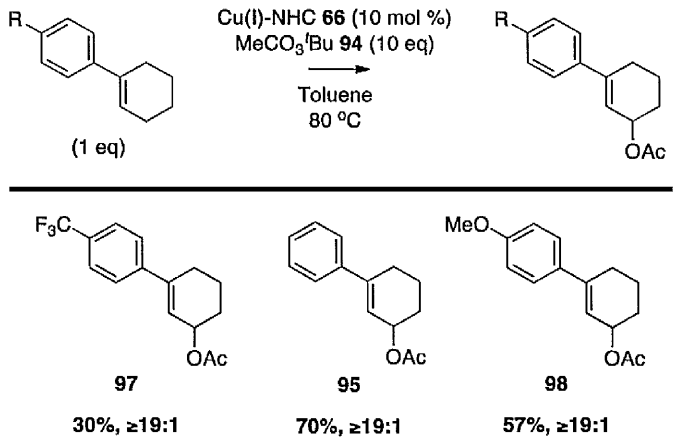
Table 1.9 *Further Optimisation using tert-Butyl Peracetate 94.*[a]

Entry	Alkene 89 (eq)	Perester 94 (eq)	Cu(I)-NHC (mol %)	Solvent	Yield 95+96[b] (%)	95:96[c]
1	5	1	**49** (5)	Benzene	57	4:1
2	2	1	**49** (5)	Benzene	37	4:1
3	5	1	**49** (10)	Benzene	57	3:1
4	1	3	**49** (10)	Benzene	43	11:1
5	1	5	**49** (10)	Benzene	56	9:1
6	1	10	**49** (10)	Benzene	61	6:1
7	1	5	**49** (10)	Toluene	32	12:1
8	1	10	**49** (10)	Toluene	78	19:1
9	***1***	***10***	***66 (10)***	***Toluene***	***70***	***>19:1***

[a]Reactions were performed on 0.25 mmol scale. [b]Isolated yields. [c]Determined by ^{1}H-NMR on crude mixtures.

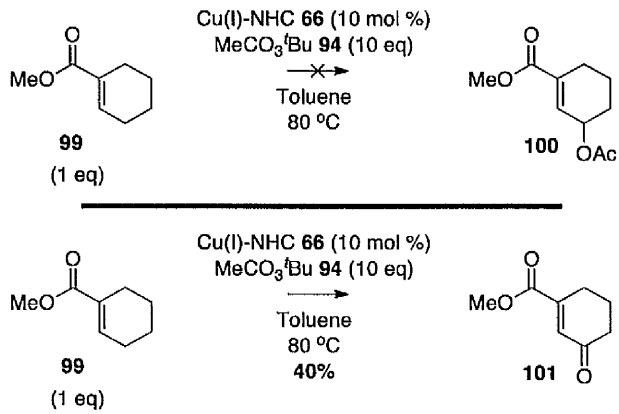
1.3.3. Scope and Limitations

Scheme 1.23 highlights the scope of the regioselective copper(I)-NHC-catalysed allylic oxidation using the *tert*-butyl peracetate **94** to furnish the allylic acetates **95**, **97** and **98** with variable yield, but excellent selectivity. The reaction was limited to aryl-substituted cyclohexenes, as deviation from these resulted in several side-products.



Scheme 1.23 *Scope of Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation.*

The copper(I)-NHC-catalysed allylic oxidation of methyl-1-cyclohexene carboxylate **99** with *tert*-butyl peracetate **94** did not furnish the expected allylic ester **100** but the 1,4-enedione **101** in 40% yield (Scheme 1.24). The formation of this enone **101** has been previously documented using other metal-catalysts and oxidants, and will be discussed in the next chapter (*vide infra*).[48]

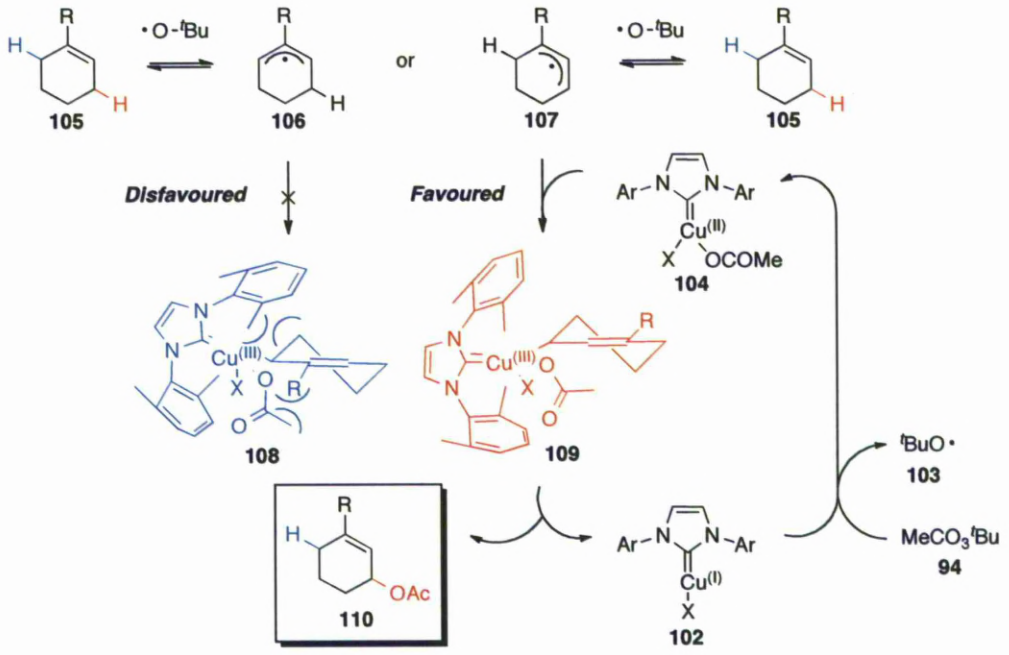


Scheme 1.24 *Enone Side-Product **101** from Allylic Oxidation of Methyl-1-Cyclohexene Carboxylate **99**.*

1.3.4. Proposed Mechanism for Copper(I)-NHC-Catalysed Allylic Oxidation

The high regioselectivities for this transformation are unique to the copper(I)-NHC system, since the *bis*-oxazoline and pybox ligands are inefficient in generating the allylic esters selectively.[24,46] A modified mechanism for regioselective copper(I)-

NHC-catalysed allylic oxidation is outlined in Scheme 1.25. Homolytic cleavage of *tert*-butyl peracetate by the copper(I)-NHC catalyst **102**, generates the *tert*-butoxy radical **103** and the copper(II)-NHC-carboxylate **104**.



Scheme 1.25 *Proposed Mechanism for the Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation using tert-Butyl peracetate* ***94****.*

The *tert*-butoxy radical **103** can undergo a reversible hydrogen abstraction of the two allylic hydrogens of the tri-substituted alkene **105** to furnish the allyl radicals **106** or **107**. The formation of the copper(III)-intermediate **108** would be disfavoured because of the steric interaction of the alkene substitution and the NHC ligand, whilst the formation of the copper(III)-intermediate **109** is more favourable. It was envisaged that the radical **107** is syphoned through to the intermediate **109**, whereas the radical **106** is re-protonated and recycled. Facile reductive elimination of the unstable copper(II)-intermediate **109** affords the allylic acetate **110** and the regeneration of the copper(I)-NHC catalyst **102**.

1.4. Conclusions

In conclusion, the examination of copper(I)-NHC-catalysed allylic oxidation of cycloalkenes has been explored. These bench stable catalysts, prepared from readily available and cost-effective materials, in a one-pot procedure, provide a number of advantages over conventional copper(I) salts. For instance, the enhanced reactivity in the Kharasch-Sosnovsky reaction makes these catalysts a viable alternative for they are effective in the preparation of allylic esters. Although, the enantioselective allylic oxidation reaction was poor, there is a plethora of chiral NHC ligands, which may provide improved selectivity. During the optimisation of the Kharasch-Sosnovsky reaction, some mechanistic insights into the optimal copper(I)-NHC catalyst have been uncovered, which translate to the effective regioselective allylic oxidation of tri-substituted cycloalkenes. The allylic oxidation of tri-substituted cycloalkenes into the corresponding allylic esters is often problematic, however the copper(I)-NHC-catalysed system provides a new reaction manifold. Nevertheless, the transformation is still limited, especially with acyclic and non-aryl substituted cycloalkenes. A modified mechanism for the regioselective copper(I)-NHC-catalysed allylic oxidation reaction, explains the origin of the high regiocontrol through catalyst/ligand control. Finally, the copper(I)-NHC-catalysed allylic oxidation of cycloalkenes with *tert*-butyl peracetate **94** also provides an enone product, the origin of which will be described in the following chapter (*vide infra*).

1.5 Experimental

1.5.1. General

Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} pre-coated silica gel plates. Visualisation was accomplished with a UV light and/or a $KMnO_4$ solution. Flash column chromatography (FCC) was performed using Merck Silica Gel 60 (230-400 mesh). Solvents for extraction and FCC were technical grade. Reported solvent mixtures for both TLC and FCC were volume/volume mixtures.

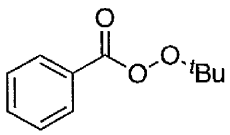
^{1}H-NMR and ^{13}C-NMR were recorded on Bruker DRX-500 NMR spectrometers in the indicated deuterated solvents. For ^{1}H-NMR, $CDCl_3$ was set to 7.26 ppm ($CDCl_3$ singlet) and for ^{13}C-NMR to 77.16 ppm ($CDCl_3$ center of triplet). All values for ^{1}H-NMR and ^{13}C-NMR chemical shifts for deuterated solvents were obtained from Cambridge Isotope Labs. Data are reported in the following order: chemical shift in ppm (δ) (multiplicity, which are indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); assignment of 2nd order pattern, if applicable; coupling constants (*J*, Hz); integration. All ^{13}C-NMR spectra were reported using descriptor (*o*) and (*e*), refers to whether the peak is odd or even, respectively, and correlates to an attached proton test (APT) experiment. Infrared spectra (IR) were obtained on Perkin-Elmer spectrum one series FTIR spectrometer. Peaks are reported in cm^{-1} with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak). Mass spectra were performed by the Department of Chemistry, Liverpool Mass Spectroscopy Department and EPSRC National Mass Spectrometry Service Centre, Swansea. High-resolution electron-impact (EI ionisation voltages of 70 eV), chemical ionisation (CI, reagent gas CH_4) and electrospray (ESI) mass spectra were obtained on a TermoFinnigan MAT 95 XP spectrometer.

Unless otherwise indicated all reactions were carried out in flame-dried glassware and under an atmosphere of argon. Syringes and needles were oven-dried and then cooled in a desiccator. Dichloromethane (DCM), diethyl ether (Et_2O), toluene (PhMe), benzene (PhH), hexane and tetrahydrofuran (THF) were dried over alumina column solvent system using the method of Grubbs. Acetonitrile (MeCN) was used directly from Acros, as extra dry over 4Å molecular sieves. Dimethylsulfoxide (DMSO) was purchased from Fischer chemical company and used without further purification. All starting materials were purchased from Acros, Aldrich, Alfa Aesar or Strem chemical companies and used without further purification unless otherwise noted.

1.5.2. Experimental Procedures

General procedure for the preparation of the peresters:

To a stirred solution of dichloromethane (5 mL) and pyridine (0.97 mL, 12 mmol) at 0 °C was added the corresponding acid chloride (10 mmol) dropwise. The reaction mixture was stirred for 10 minutes at 0 °C, to which *tert*-butyl hydroperoxide (5.5 M in decane, 2.18 mL, 12 mmol) was added dropwise. The reaction mixture was warmed slowly to room temperature and stirred for 6 hours. The reaction was then diluted with dichloromethane (50 mL), washed with water (50 mL) and brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated under vacuum (bath temperature kept below 30 °C) to yield a crude residue. The crude residue was purified using flash chromatography on silica gel (diethyl ether/hexane) to yield the desired perester as an oil/solid.



***tert*-Butyl benzoperoxoate 28.**[49]

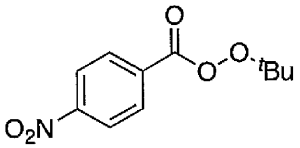
Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Diethyl ether

= 95:5).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using benzoyl chloride in 91%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 6.9 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 1.42 (s, 9H).

IR (Neat) 2982 (w), 2935 (w), 1752 (s), 1611 (m), 1237 (s) cm^{-1}.



***tert*-Butyl 4-nitrobenzoperoxoate 35.**[49]

Colour and state: Pale yellow solid. R_f = 0.4 (Hexane:Diethyl ether = 90:10).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 4-nitrobenzoyl chloride in 96%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 1.43 (s, 9H).

IR (Neat) 3127 (w), 2984 (w), 2934 (w), 1755 (s), 1608 (w), 1524 (s), 1346 (s), 1247 (s) cm^{-1}.

General procedure for the preparation of the copper-NHC catalysts:[50]

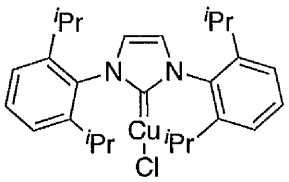
To a stirred solution of amine (44 mmol) in 1-propanol/H_2O (4:1, 10 mL) was added glyoxal (20 mmol) in 1-propanol (5 mL). The reaction mixture was stirred at 60 °C for 1-16 hours and cooled to ambient temperature. Distilled water (20 mL) was added to the mixture and the precipitation was filtered under vacuum. The solid was dried under high vacuum overnight to yield pure *bis*-imine solid (95%).

To a stirred solution of chloromethyl ethyl ether (15 mmol) in THF (7.5 mL) was added the *bis*-imine (15 mmol) dissolved in THF (5 mL) with a drop of catalytic water. The reaction mixture was stirred at 40 °C for 16 hours and cooled to ambient

temperature. The black reaction mixture was filtered under vacuum and the crude solid was washed with EtOAc (100 mL) to yield pure imidazolium chloride solid (70%).

To a flask in the glove-box was added imidazolium salt (5 mmol), sodium *tert*-butoxide (5.5 mmol) and copper(I) halide (5.5 mmol). The reaction was charged with THF (50 mL) and stirred at room temperature for 6 hours. The reaction mixture was filtered through a celite plug and the filtrate was concentrated under vacuum to yield a crude solid. The crude solid was recrystallised from CH_2Cl_2/EtOAc to yield pure copper-NHC solid (60%).

To a flask in the glove-box was added copper-NHC (1 mmol) and silver salt (1.1 mmol). The reaction was charged with MeCN (10 mL) and stirred at rt for 1 hours. The reaction mixture was filtered through a celite plug and the filtrate was concentrated under vacuum to yield pure copper-NHC solid (75%).



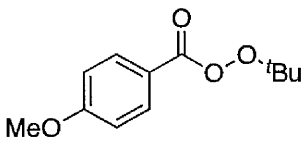
(1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-ylidene)copper(I) chloride 49.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 7.8 Hz, 4H), 7.13 (s, 2H), 2.55 (sept, J = 6.9 Hz, 4H), 1.30 (d, J = 6.9 Hz, 12H), 1.23 (d, J = 6.9 Hz, 12H).

IR (Neat) 3054 (w), 2964 (w), 2871 (w), 1594 (w), 1468 (w), 1265 (m) cm^{-1}.



***tert*-Butyl 4-methoxybenzoperoxoate 52.**[49]

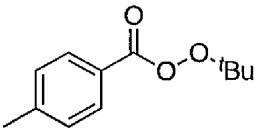
Colour and state: Colorless oil. R_f = 0.4 (Hexane:Diethyl

ether = 90:10).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 4-methoxybenzoyl chloride in 92%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 1.41 (s, 9H).

IR (Neat) 2981 (w), 2936 (w), 2842 (w), 1747 (s), 1605 (s), 1510 (m), 1242 (s) cm^{-1}.



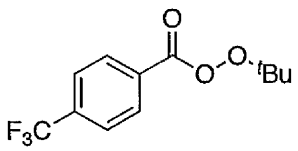
***tert*-Butyl 4-methylbenzoperoxoate 53.**[49]

Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Diethyl ether = 95:5).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 4-methylbenzoyl chloride in 92%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 2.42 (s, 3H), 1.41 (s, 9H).

IR (Neat) 3065 (w), 2982 (w), 2936 (w), 1755 (s), 1600 (w), 1451 (m), 1233 (s) cm^{-1}.



***tert*-Butyl 4-(trifluoromethyl)benzoperoxoate 54.**

Colour and state: Pale yellow oil. R_f = 0.3 (Hexane:Diethyl ether = 95:5).

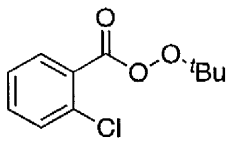
Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 4-(trifluoromethyl)benzoyl chloride in 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.33 (e), 135.01 (e, q, $J_{C\text{-}F}$ = 32.8 Hz, CCF), 131.14 (e), 129.71 (o), 125.83 (o, q, $J_{C\text{-}F}$ = 3.6 Hz, CCCF), 123.57 (e, q, $J_{C\text{-}F}$ = 272.4 Hz, CF), 84.58 (e), 26.35 (o).

IR (Neat) 2984 (w), 2938 (w), 1763 (s), 1586 (w), 1412 (m), 1323 (s), 1235 (s) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{12}H_{17}F_3O_3N$ 280.11605, found 280.11680.



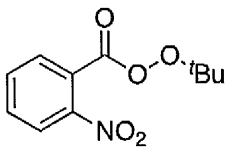
***tert*-Butyl 2-chlorobenzoperoxoate 55.**[49]

Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Diethyl ether = 95:5).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 2-chlorobenzoyl chloride in 93%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 6.9 Hz, 1H), 7.44-7.48 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 1.42 (s, 9H).

IR (Neat) 2982 (w), 2936 (w), 1769 (s), 1591 (m), 1436 (m), 1367 (m), 1229 (s) cm^{-1}.



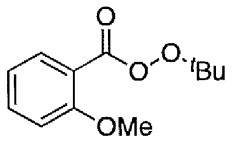
***tert*-Butyl 2-nitrobenzoperoxoate 56.**[49]

Colour and state: Pale yellow solid. R_f = 0.4 (Hexane:Diethyl ether = 90:10).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 2-nitrobenzoyl chloride in 95%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (t, J = 1.8 Hz, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 1.44 (s, 9H).

IR (Neat) 3092 (w), 2983 (w), 2937 (w), 1759 (s), 1617 (w), 1533 (s), 1440 (w), 1349 (s), 1234 (s) cm^{-1}.



***tert*-Butyl 2-methoxybenzoperoxoate 57.**[49]

Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Diethyl ether = 90:10).

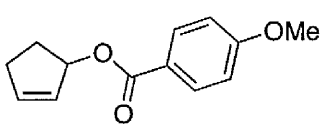
Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the peresters using 2-methoxybenzoyl chloride in 93%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 1.42 (s, 9H).

IR (Neat) 2981 (w), 2938 (w), 1742 (s), 1600 (m), 1490 (m), 1366 (m), 1254 (s) cm^{-1}.

General procedure for the copper(I)-NHC-catalysed allylic oxidation:

To a flask was added copper-NHC-catalyst **70** (0.0125 mmol) and MeCN (1 mL). The reaction mixture was stirred for 10 minutes and the alkene/heterocycle (2.5 mmol) was added, followed by the perester (0.25 mmol). The reaction was stirred at 45 °C for the allocated time and cooled to ambient temperature. The reaction mixture was concentrated under vacuum and the residue was purified using flash chromatography on silica gel (diethyl ether/hexane) to yield pure desired product.



Cyclopent-2-enyl 4-methoxybenzoate 58.[51]

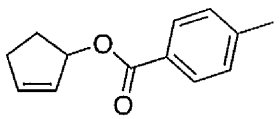
Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 30:70).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **52** and cyclopentene in 70%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 6.15-6.14 (m, 1H), 5.94-5.91 (m, 2H), 3.85 (s, 3H), 2.62-2.56 (m, 1H), 2.43-2.34 (m, 2H), 1.98-1.91 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.46, 163.33, 137.60, 131.71, 129.69, 123.25, 113.61, 80.90, 55.55, 31.31, 30.06.

IR (Neat) 2935 (w), 2841 (w), 1703 (s), 1605 (s), 1510 (m), 1254 (s) cm^{-1}.



Cyclopent-2-enyl 4-methybenzoate 59.

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 10:90).

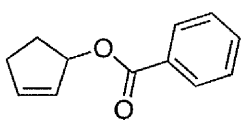
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **53** and cyclopentene in 77%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 6.16-6.14 (m, 1H), 5.95-5.92 (m, 2H), 2.63-2.56 (m, 1H), 2.44-2.35 (m, 5H), 1.99-1.92 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.77, 143.48, 137.68, 129.72, 129.60, 129.10, 128.05, 81.02, 31.31, 30.03, 21.77.

IR (Neat) 2924 (w), 2855 (w), 1709 (s), 1611 (m), 1452 (w), 1269 (s) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{13}H_{18}O_2N$ 220.13375, found 220.13448.



Cyclopent-2-enyl benzoate 60.[51]

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane =

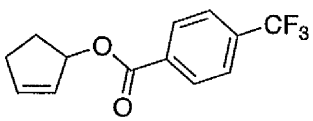
10:90).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **28** and cyclopentene in 74%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 6.17-6.16 (m, 1H), 5.96-5.94 (m, 2H), 2.63-2.52 (m, 1H), 2.44-2.36 (m, 2H), 2.00-1.94 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.70, 137.84, 132.88, 130.81, 129.70, 129.50, 128.40, 81.25, 31.32, 30.02.

IR (Neat) 2937 (w), 2855 (w), 1711 (s), 1602 (w), 1451 (m), 1269 (s) cm^{-1}.



Cyclopent-2-enyl 4-(trifluoromethyl)benzoate 61.

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 20:80).

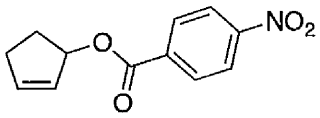
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **54** and cyclopentene in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 6.20-6.18 (m, 1H), 5.98-5.94 (m, 2H), 2.65-2.57 (m, 1H), 2.46-2.37 (m, 2H), 2.02-1.95 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.48 (e), 138.37 (o), 134.30 (e, q, $J_{C\text{-}F}$ = 32.3 Hz, CCF), 130.12 (0), 129.14 (o), 125.45 (o, q, $J_{C\text{-}F}$ = 3.7 Hz, CCCF), 123.57 (e, q, $J_{C\text{-}F}$ = 272.4 Hz, CF), 81.99 (o), 31.34 (e), 29.99 (e).

IR (Neat) 2941 (w), 2858 (w), 1717 (s), 1586 (w), 1411 (m), 1270 (s), 1166 (m), 1099 (s), 1066 (m) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{13}H_{15}F_3O_2N$ 274.10549, found 274.10572.



Cyclopent-2-enyl 4-nitrobenzoate 62.[51]

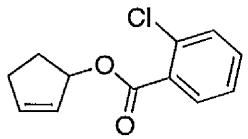
Colour and state: Colourless solid. R_f = 0.4 (Et_2O:Hexane = 20:80).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **35** and cyclopentene in 87%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H), 6.22-6.21 (m, 1H), 5.99-5.94 (m, 2H), 2.65-2.57 (m, 1H), 2.47-2.39 (m, 2H), 2.03-1.96 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.76, 150.54, 138.70, 136.21, 130.82, 128.87, 123.59, 82.46, 31.33, 29.93.

IR (Neat) 3112 (w), 2948 (w), 2862 (w), 1708 (s), 1608 (m), 1524 (s), 1280 (s) cm^{-1}.



Cyclopent-2-enyl 2-chlorobenzoate 63.

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 10:90).

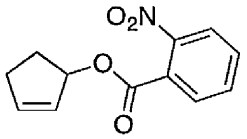
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **55** and cyclopentene in 73%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 6.19-6.17 (m, 1H), 5.97-5.95 (m, 2H), 2.63-2.54 (m, 1H), 2.43-2.35 (m, 2H), 2.05-1.96 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.88, 138.33, 133.61, 132.38, 131.32, 131.06, 130.83, 129.11, 126.63, 81.98, 31.29, 29.92.

IR (Neat) 3063 (w), 2943 (w), 2854 (w), 1721 (s), 1592 (m), 1287 (s), 1247 (s) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{12}H_{15}ClO_2N$ 240.07913, found 240.07973.



Cyclopent-2-enyl 2-nitrobenzoate 64.[52]

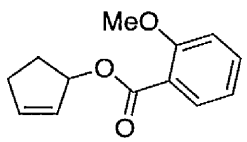
Colour and state: Colourless solid. R_f = 0.4 (Et_2O:Hexane = 20:80).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **56** and cyclopentene in 58%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (t, *J* = 1.8 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 6.22-6.20 (m, 1H), 6.00-5.94 (m, 2H), 2.67-2.58 (m, 1H), 2.47-2.38 (m, 2H), 2.06-1.97 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.48, 139.03, 133.00, 131.61, 129.93, 128.43, 128.30, 123.96, 83.06, 31.27, 29.44.

IR (Neat) 3086 (w), 2919 (w), 2851 (w), 1716 (s), 1616 (m), 1531 (s), 1259 (s) cm^{-1}.



Cyclopent-2-enyl 2-methoxybenzoate 65.

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 30:70).

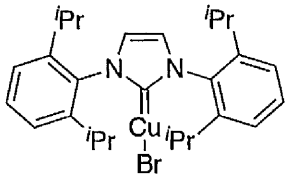
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **57** and cyclopentene in 56%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.15-6.13 (m, 1H), 5.96-5.93 (m, 2H), 3.90 (s, 3H), 2.62-2.54 (m, 1H), 2.42-2.34 (m, 2H), 1.99-1.93 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.16, 159.29, 137.67, 133.40, 131.61, 129.62, 120.66, 120.16, 112.13, 81.03, 56.11, 31.30, 30.02.

IR (Neat) 3056 (w), 2942 (w), 2854 (w), 1719 (s), 1601 (m), 1250 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{13}H_{15}O_3$ 219.10212, found 219.10153.



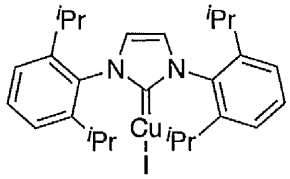
(1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-ylidene)copper(I) bromide 66.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 7.8 Hz, 4H), 7.14 (s, 2H), 2.56 (sept, J = 6.5 Hz, 4H), 1.30 (d, J = 6.5 Hz, 12H), 1.23 (d, J = 6.5 Hz, 12H).

IR (Neat) 3054 (w), 2967 (w), 2869 (w), 1578 (w), 1469 (w), 1265 (m) cm^{-1}.



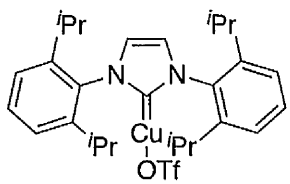
(1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-ylidene)copper(I) iodide 67.[50]

Colour and state: Colourless solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, J = 7.8 Hz, 2H), 7.14 (d, J = 7.8 Hz, 4H), 7.00 (s, 2H), 2.29 (sept, J = 6.8 Hz, 4H), 1.03 (d, J = 6.8 Hz, 12H), 0.83 (d, J = 6.8 Hz, 12H).

IR (Neat) 3074 (w), 2965 (m), 2871 (w), 1565 (w), 1460 (m), 1279 (w) cm^{-1}.



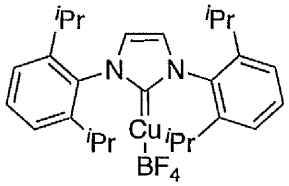
(1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-ylidene)copper(I) trifluoromethanesulfonate 68.[50]

Colour and state: Colourless solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (t, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 4H), 7.20 (s, 2H), 2.51 (sept, J = 6.8 Hz, 4H), 1.27 (d, J = 6.8 Hz, 12H), 1.23 (d, J = 6.8 Hz, 12H).

IR (Neat) 2964 (m), 2929 (w), 2872 (w), 1595 (w), 1470 (m), 1276 (m), 1236 (s), 1200 (s), 1177 (s) cm^{-1}.



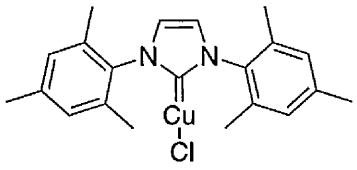
(1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-ylidene)copper(I) tetrafluoroborate 69.[50]

Colour and state: Colourless solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, J = 7.8 Hz, 2H), 7.12 (d, J = 7.8 Hz, 4H), 7.09 (s, 2H), 2.25 (sept, J = 6.8 Hz, 4H), 1.27-1.24 (m, 24H).

IR (Neat) 2963 (m), 2871 (w), 1594 (w), 1469 (m) 1058 (s) cm^{-1}.



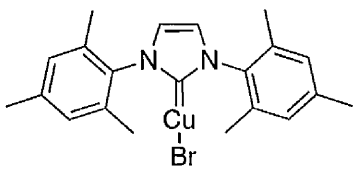
(1,3-dimesityl-1H-imidazol-2(3H)-ylidene)copper(I) chloride 70.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (s, 2H), 7.00 (s, 4H), 2.35 (s, 6H), 2.10 (s, 12H).

IR (Neat) 2977 (w), 2948 (w), 2914 (w), 1608 (w), 1486 (s), 1235 (m) cm^{-1}.



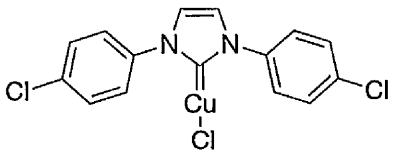
(1,3-dimesityl-1H-imidazol-2(3H)-ylidene)copper(I) bromide 71.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (s, 2H), 7.00 (s, 4H), 2.35 (s, 6H), 2.11 (s, 12H).

IR (Neat) 2975 (w), 2946 (w), 2914 (w), 1608 (w), 1486 (m), 1235 (m) cm^{-1}.



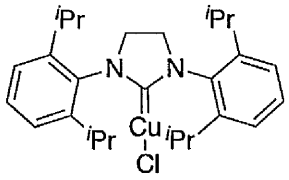
(1,3-bis(4-chlorophenyl)-1H-imidazol-2(3H)-ylidene)copper(I) chloride 72.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 4H), 7.53 (d, J = 8.3 Hz, 4H), 7.39 (s, 2H).

IR (Neat) 3003 (w), 3054 (w), 2982 (w), 1594 (w), 1492 (s), 1409 (m), 1277 (m) cm^{-1}.



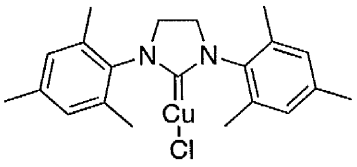
(1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)copper(I) chloride 73.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, J = 7.8 Hz, 2H), 7.25 (d, J = 7.8 Hz, 4H), 4.02 (s, 4H), 3.06 (sept, J = 6.8 Hz, 4H), 1.37 (d, J = 6.8 Hz, 12H), 1.34 (d, J = 6.8 Hz, 12H).

IR (Neat) 2962 (m), 2928 (w), 2868 (m), 1591 (w), 1482 (s), 1268 (s) cm^{-1}.



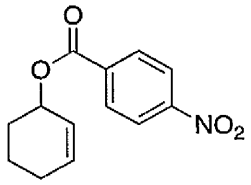
(1,3-dimesitylimidazolidin-2-ylidene)copper(I) chloride 74.[50]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 4H), 3.95 (s, 4H), 2.32 (s, 6H), 2.30 (s, 12H).

IR (Neat) 2973 (w), 2948 (w), 2917 (w), 1609 (w), 1485 (s), 1262 (s) cm^{-1}.



Cyclohex-2-enyl 4-nitrobenzoate 75.

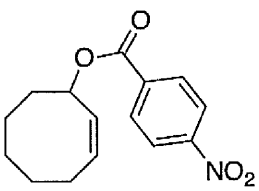
Colour and state: Colourless solid. R_f = 0.4 (Et_2O:Hexane = 20:80). mp = 90-92 °C.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **35** and cyclohexene in 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H), 6.07-6.04 (m, 1H), 5.85-5.83 (m, 1H), 5.54 (m, 1H), 2.19-2.14 (m, 1H), 2.09-1.97 (m, 2H), 1.94-1.80 (m, 2H), 1.77-1.69 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.41, 150.53, 136.30, 133.75, 130.81, 125.07, 123.57, 69.90, 28.39, 25.01, 18.91.

IR (Neat) 2939 (w), 2867 (w), 1719 (s), 1607 (w), 1527 (s), 1272 (s) cm^{-1}.



(*Z*)-Cyclooct-2-en-1-yl 4-nitrobenzoate 76.[51]

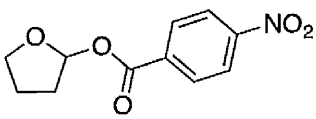
Colour and state: Colourless oil. R_f = 0.5 (Et_2O:Hexane = 20:80).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **35** and cyclooctene in 46%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H), 5.95-5.91 (m, 1H), 5.76 (ddt, J = 9.9, 6.8, 1.6 Hz, 1H), 5.61 (ddd, J = 10.8, 7.0, 1.1 Hz, 1H), 2.37-2.29 (m, 1H), 2.21-2.16 (m, 1H), 2.09-2.03 (m, 1H), 1.77-1.40 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.22, 150.60, 136.27, 130.82, 130.65, 130.05, 123.63, 74.35, 35.20, 28.91, 26.58, 25.98, 23.48.

IR (Neat) 2925 (m), 2859 (w), 1716 (s), 1605 (w), 1521 (s), 1276 (s) cm^{-1}.



Tetrahydrofuran-2-yl 4-nitrobenzoate 77.

Colour and state: Colourless solid. R_f = 0.3 (Et_2O:Hexane = 50:50). mp = 74-76 °C.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalysed allylic oxidation using perester **35** and tetrahydrofuran in 73%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H), 4.17 (dt, J = 8.2, 5.0 Hz, 1H), 4.04 (t, J = 7.9 Hz, 1H), 2.24-2.01 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.24, 135.92, 130.90, 123.65, 100.85, 69.52, 32.48, 29.84, 23.02.

IR (Neat) 2919 (w), 1726 (s), 1607 (w), 1527 (s), 1272 (s) cm^{-1}.

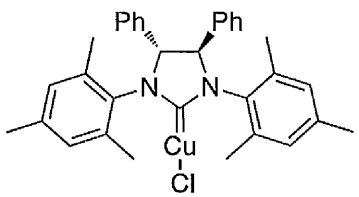
HRMS (ESI, $[M+Na]^+$) calcd for $C_{11}H_{11}NO_5Na$ 260.0535, found 260.0531.

General procedure for the preparation of the chiral copper-NHC catalysts:[44]

To a flask in the glove-box was added palladium acetate (0.25 mmol), BINAP (0.6 mmol) and sodium *tert*-butoxide (15 mmol). The flask was charged with toluene (17 mL) and stirred for 20 minutes. Enantiopure amine (5 mmol) and aryl bromide (10.5 mmol) were added to the reaction mixture and stirred at 110 °C for 16 hours. The reaction was then cooled to ambient temperature and concentrated under vacuum to minimum volume. The reaction residue was purified using flash chromatography on silica gel (CH_2Cl_2:MeOH) to yield pure *bis*-imine solid.

To a flask was added *bis*-imine (2 mmol), ammonium tetrafluoroborate (2 mmol) and triethyl orthoformate (20 mmol). The reaction was stirred at 120 °C for 16 hours and cooled to ambient temperature. The crude product was purified using flash chromatography on silica gel (CH_2Cl_2:MeOH) to yield pure chiral NHC salt.

To a flask in the glove-box was added chiral NHC salt (1 mmol), sodium *tert*-butoxide (1.1 mmol) and copper(I) halide (1.1 mmol). The reaction was charged with THF (10 mL) and stirred at room temperature for 6 hours. The reaction mixture was filtered through a celite plug and the filtrate was concentrated under vacuum to yield a crude solid. The crude solid was recrystallised from CH_2Cl_2/EtOAc to yield pure chiral copper-NHC solid.



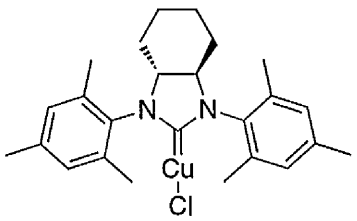
((4R,5R)-1,3-dimesityl-4,5-diphenylimidazolidin-2-ylidene)copper(I) chloride 78.[44]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the chiral copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.6 Hz, 4H), 7.09 (d, J = 7.2 Hz, 4H), 6.81 (b, 2H), 6.67 (b, 2H), 5.44 (s, 2H), 2.37 (s, 6H), 1.99 (s, 6H), 1.52 (s, 6H).

IR (Neat) 3093 (w), 3035 (w), 2967 (w), 1688 (w), 1595 (w), 1492 (s), 1276 (m) cm^{-1}.



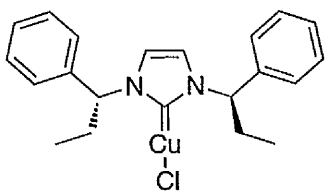
((3aR,7aR)-1,3-dimesityl-1H-benzo[d]imidazol-2(3H,3aH,4H,5H,6H,7H,7aH)-ylidene)copper(I) chloride 79.[44]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the chiral copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, J = 15.6 Hz, 4H), 3.59-3.57 (m, 2H), 2.30-2.27 (m, 18H), 1.87-1.84 (m, 4H), 1.52-1.48 (m, 2H), 1.28-1.20 (m, 2H).

IR (Neat) 3093 (w), 2938 (w), 2865 (w), 1686 (w), 1594 (w), 1491 (s), 1276 (m) cm^{-1}.



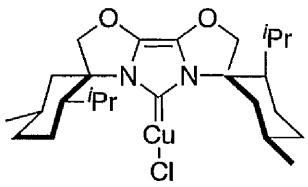
(1,3-bis((R)-1-phenylpropyl)-1H-imidazol-2(3H)-ylidene)copper(I) chloride 80.[44]

Colour and state: Pale yellow solid.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the chiral copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.30 (m, 10H), 6.90 (s, 2H), 5.53 (t, J = 6.9 Hz, 2H), 2.34-2.17 (m, 4H), 0.92 (t, J = 7.2 Hz, 6H).

IR (Neat) 3091 (w), 2965 (w), 2874 (w), 1686 (w), 1594 (w), 1493 (s), 1276 (m) cm^{-1}.



IBiox[(-)-menthyl]copper(I) chloride 81.[33,34]

Colour and state: Pale yellow solid.

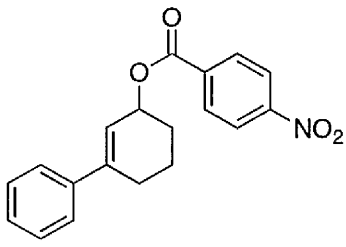
Representative Experimental Procedure: Prepared in accordance to the general procedure for the preparation of the chiral copper-NHC catalysts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (d, J = 9.4 Hz, 2H), 4.42 (d, J = 9.4 Hz, 2H), 3.16-3.32 (m, 2H), 2.20-2.35 (m, 2H), 2.02-2.15 (m, 4H), 1.89-1.94 (m, 2H), 1.67-1.73 (m, 2H), 1.20-1.38 (m, 4H), 0.93-0.95 (m, 14H), 0.30 (d, J = 6.8 Hz, 6H).

IR (Neat) 2958 (w), 2924 (m,), 2856 (w), 1750 (s), 1432 (w), 1294 (vs) cm^{-1}.

General procedure for the regioselective copper(I)-NHC-catalysed allylic oxidation:

To a flask was added copper-NHC (10 mol %) and PhMe (2.5 mL). The reaction mixture was stirred for 10 minutes and alkene (0.25 mmol) was added, followed by perester (2.5 mmol). The reaction was stirred at 80 °C for 12 hours and cooled to ambient temperature. The reaction mixture purified using flash chromatography on silica gel (diethyl ether/hexane) to yield pure desired product.



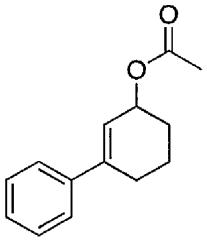
3-Phenycyclohex-2-enyl 4-nitrobenzoate 90.[53]

Colour and state: Colourless solid. R_f = 0.5 (Et_2O:Hexane = 20:80).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the regioselective copper(I)-NHC-catalysed allylic oxidation using perester **35** and 1-phenylcyclohexene in 38%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 6.22 (m, 1H), 5.75 (m, 1H), 2.62 (m, 1H), 2.45 (m, 1H), 1.98 (m, 4H).

IR (Neat) 2938 (w), 2869 (w), 1715 (s), 1607 (w), 1524 (s), 1263 (s) cm^{-1}.



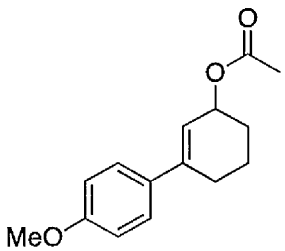
3-Phenycyclohex-2-enyl acetate 95.[54]

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 5:95).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the regioselective copper(I)-NHC-catalysed allylic oxidation using *tert*-butyl peracetate and 1-phenylcyclohexene in 70%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 7.2 Hz, 2H), 6.08 (m, 1H), 5.46 (m, 1H), 2.53 (m, 1H), 2.38 (m, 1H), 2.08 (s, 3H), 1.93 (m, 2H), 1.79 (m, 2H).

IR (Neat) 2936 (w), 2867 (w), 1728 (s), 1599 (w), 1235 (s) cm^{-1}.



4'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl acetate 97.

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 10:90).

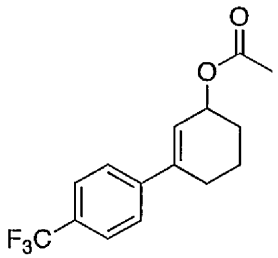
Representative Experimental Procedure: Prepared in accordance to the general procedure for the regioselective copper(I)-NHC-catalysed allylic oxidation using *tert*-butyl peracetate and 4-methoxyphenyl-1-cyclohexene in 57%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 6.87-6.84 (m, 2H), 6.02-6.01 (m, 1H), 5.46-5.43 (m, 1H), 3.81 (s, 3H), 2.52-2.47 (m, 1H), 2.38-2.32 (m, 1H), 2.07 (s, 3H), 1.94-1.88 (m, 2H), 1.80-1.75 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.02 (e), 159.36 (e), 141.61 (e), 133.61 (e), 126.63 (o), 120.69 (o), 113.75 (o), 69.18 (o), 55.37 (o), 28.13 (e), 27.45 (e), 21.57 (o), 19.49 (e).

IR (Neat) 2942 (w), 1722 (s), 1605 (m), 1512 (m), 1373 (m), 1237 (vs), 1182 (s), 1024 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{18}O_3Na$ 269.1154, found 269.1161.



4'-(trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl acetate 98.

Colour and state: Colourless oil. R_f = 0.4 (Et_2O:Hexane = 5:95).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the regioselective copper(I)-NHC-catalysed allylic oxidation using *tert*-butyl peracetate and 4-(trifluoromethyl)phenyl-1-cyclohexene in 30%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.57 (m, 2H), 7.51-7.49 (m, 2H), 6.15-6.14 (m, 1H), 5.46-5.44 (m, 1H), 2.55-2.49 (m, 1H), 2.41-2.36 (m, 1H), 2.08 (s, 3H), 1.98-1.91 (m, 1H), 1.85-1.77 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.84 (e), 144.68 (e), 141.07 (e), 129.61 (e, q, J_{C-F} = 32.8 Hz, CCF), 124.26 (e, q, J_{C-F} = 272.0 Hz, CF), 125.81 (o), 125.32 (o, q, J_{C-F} = 3.8 Hz, CCCF), 124.51 (o), 68.72 (o), 27.89 (e), 27.32 (e), 21.38 (o), 19.40 (e).

IR (Neat) 2940 (w), 1732 (s), 1615 (w), 1324 (vs), 1234 (vs), 1163 (s), 1114 (vs), 1069 (s), 1015 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{15}O_2F_3Na$ 307.0922, found 307.0923.

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Chapter 2

Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of Alkenes to α, β-Unsaturated Ketones

2.1 Introduction

2.1.1. Background and Significance

α, β-Unsaturated ketones (enones) are an important class of compounds in organic synthesis, because they are useful substrates for a range of synthetically transformations (Fig. 2.1).[1] A myriad of methods have been developed for the synthesis of this versatile functionality, e.g. alkenylation of carbonyl groups, cross-metathesis of terminal alkenes, Horner-Wadsworth-Emmons reaction of aldehydes and the oxidation of allylic alcohols.[2] Nevertheless, there are several drawbacks to each of these methods, namely, the use of stoichiometric organometallics, expensive transition metals and reagents.

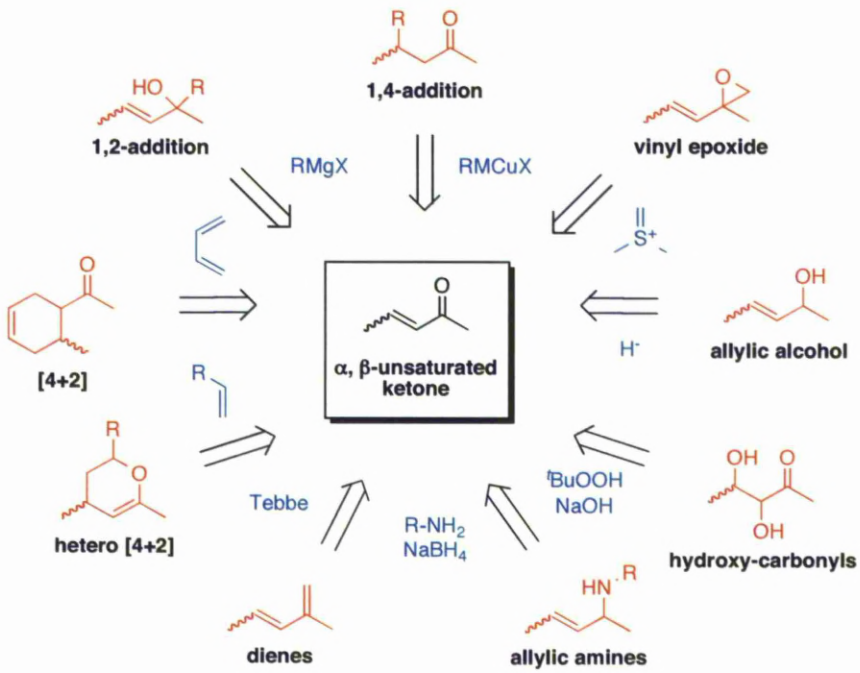
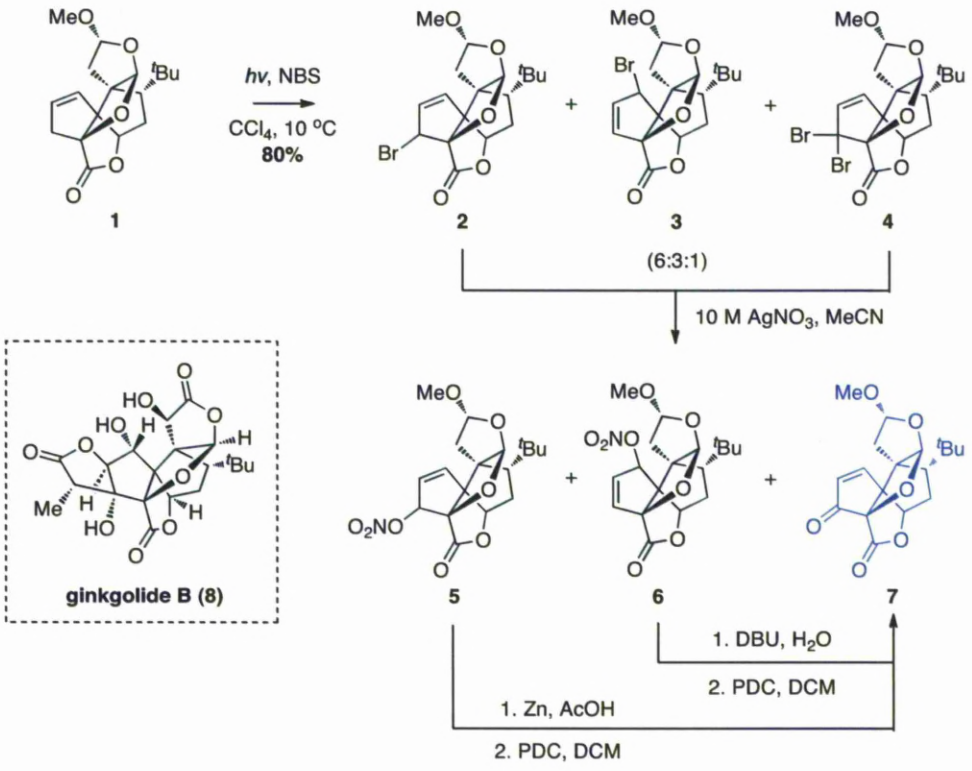


Figure 2.1 *Transformations of α, β-Unsaturated Ketones.*

The preparation of enones is not trivial and has hampered many total syntheses of natural products. For example, this problem was highlighted in the total synthesis of ginkgolide B **8**, for the conversion of the cyclopentene **1** into the *α, β*-unsaturated ketone **7** (Scheme 2.1).[3] The cyclopentene **1** was brominated under photochemical conditions to furnish the allylic bromides **2-4** in 80% overall yield, although the mixture is inconsequential to the formation of the desired enone **7**. The isomers were separated and the allylic nitrate esters **5** and **6** were converted to the enone **7** in 50% overall yield. Hence, this sequence underlined the necessity for a more direct route to this functionality.

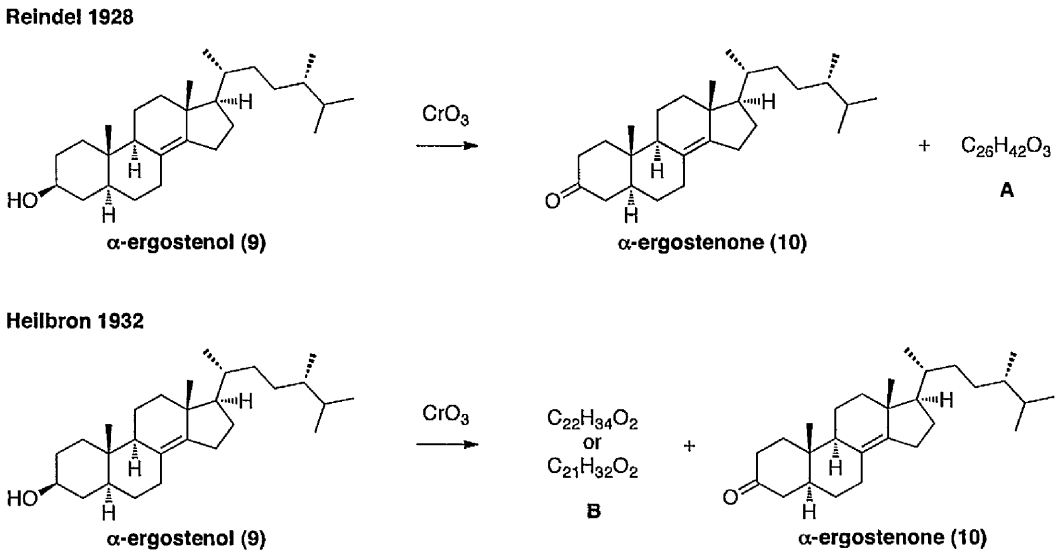


Scheme 2.1 *Corey's Enone Formation in the Total Synthesis of Ginkgolide B* ***8****.*

2.1.2. Stoichiometric Methods

The first allylic oxidation reactions of alkenes to give *α, β*-unsaturated ketones were carried out using stoichiometric selenium and chromium reagents.[4] These reagents are highly toxic, and on large scale, provide problems with waste disposal

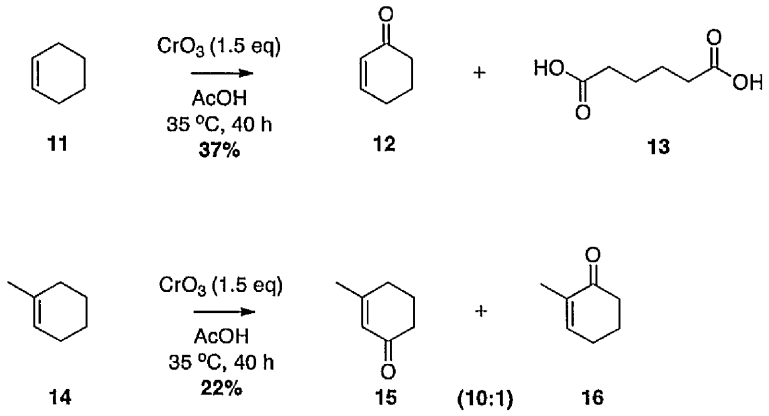
and purification. Although selenium and chromium reagents are still utilised, they are limited in the context of chemo- and regioselectivity, and thus more selective and catalytic methods have been pursued. Although the mechanism for selenium(IV) dioxide allylic oxidation is well established, the corresponding chromium(VI) variant is poorly understood by comparison.[5]



Scheme 2.2 *First Reported Chromium Oxidation.*

Chromium-mediated oxidation reactions with both stoichiometric and catalytic variants are relatively common. In 1928, Reindel reported the chromium oxidation of α-ergostenol **9** to α-ergostenone **10** using chromium anhydride (Scheme 2.2).[6] In 1932, Heilbron reported that the major product was not α-ergostenone **10** under identical conditions, but an unknown compound **B**.[7]

Whitmore *et al.* later reported that chromic anhydride and acetic acid solution effect the allylic oxidation of cyclohexene **11** to cyclohexenone **12** in 37% yield, with adipic acid **13** as the major product.[8] Interestingly, they also reported the allylic oxidation of 1-methylcyclohexene **13** under the same conditions to provide 1-methylcyclohexene-3-one **14** in 20% yield, and 1-methylcyclohexene-6-one **15** in 2% yield (Scheme 2.3).



Scheme 2.3 *CrO_3 and Acetic Acid Allylic Oxidation by Whitmore et al.*

The reasoning behind the choice of alkenes is due to the fact that cyclic allylic C-H bonds are weaker than the corresponding acyclic bonds (82.3 kcal/mol *vs.* 86.3 kcal/mol), which makes the allylic oxidation of cycloalkenes much more facile.[9] Cyclic alkenes are also preferred over acyclic alkenes due to the "cyclic activation" of the allylic hydrogens.[10a] Cyclic alkenes have the ability to align the allylic hydrogen with the double bond, thereby reducing the conformational change between the ground state and the transition state. Cyclic alkenes have enhanced reactivity over acyclic alkenes due to a combination of factors, including resonance, polar and steric effects.[10b] These features coupled with the lower bond dissociation energies; make cyclic alkenes the optimal substrates for allylic oxidation chemistry.

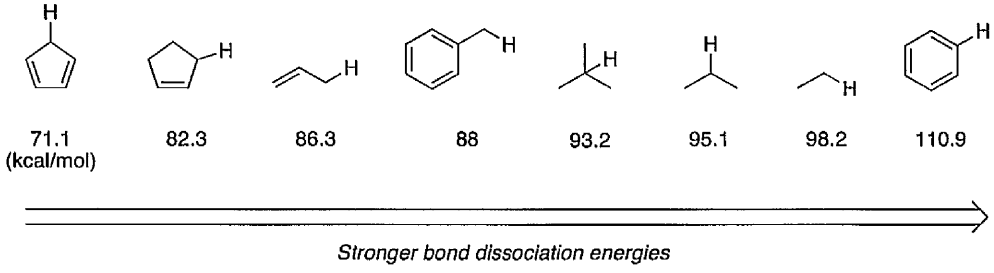
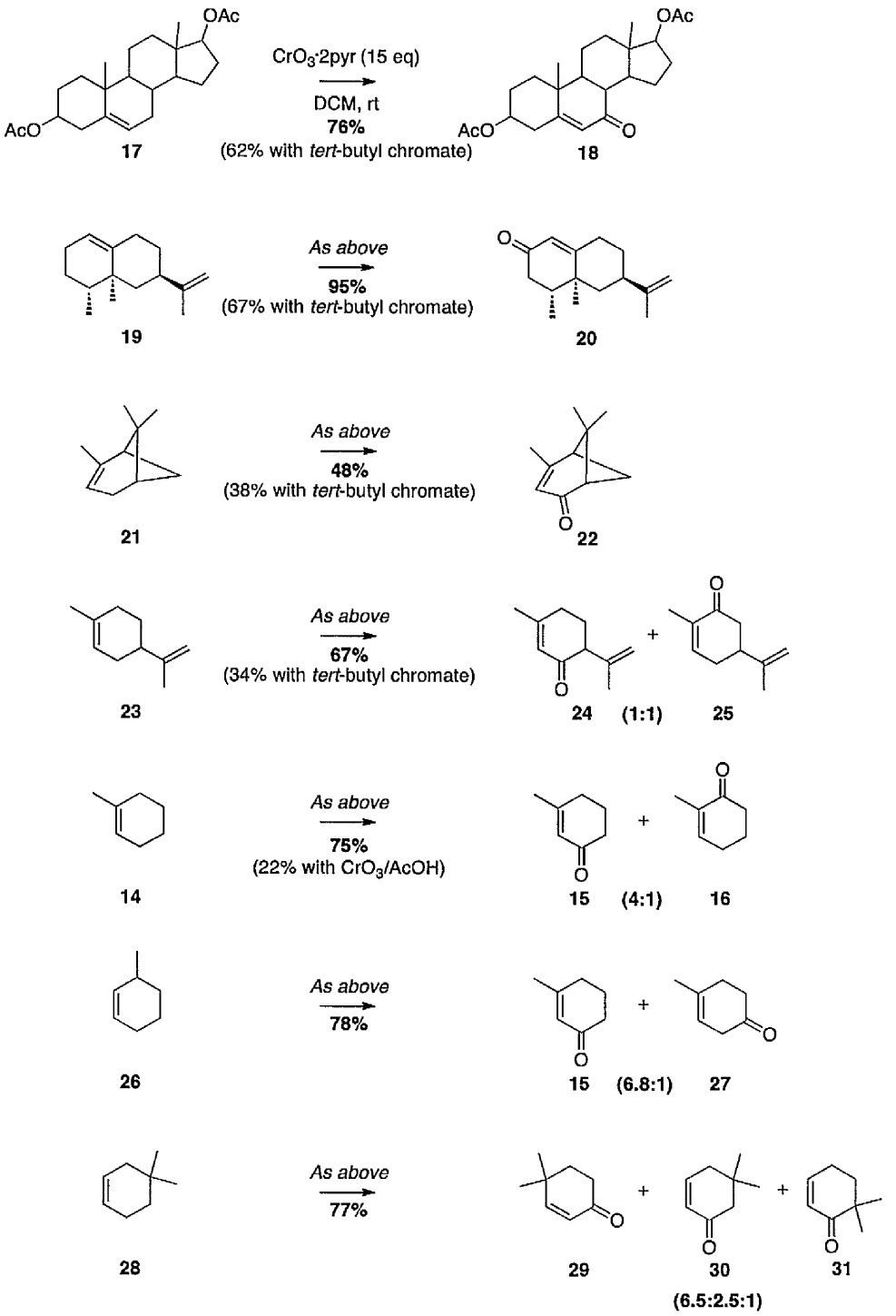


Figure 2.2 *Selected Bond Dissociation Energies (BDE's).*

In 1969, Dauben *et al.* reported the allylic oxidation of cycloalkenes with chromium trioxide-pyridine complex (Collins reagent).[11,12] Dauben subjected a wide range of substituted-alkenes to the chromium allylic oxidation and compared the yields to the previously reported methods (Scheme 2.4). For example, treatment of

the steroid **17** with the chromium trioxide-pyridine complex provided the enone **18** in 76% yield at room temperature, which compares favourably to the method using *tert*-butyl chromate (Scheme 2.4).[13]



Scheme 2.4 *Allylic Oxidation using Chromium Trioxide-Pyridine Complex.*

Alternatively, the alkenes **19** and **21** were oxidised to the enones **20** and **22** in 95% and 48% yield, respectively, in which the tertiary hydrogens on bridgehead allylic positions are not preferentially attacked due to the absence of resonance stabilisation.[14] Additionally, acyclic alkenes, for example **19** and **23**, are not oxidised (Scheme 2.4). Conformationally flexible alkenes with more than one allylic site (e.g. alkenes **14**, **23**, **26** and **28**) lead to mixtures of enones. Alkenes **14** and **23** are oxidised in good yield, albeit with poor regioselectivity. Interestingly, Dauben and Whitmore report contrasting selectivity for the formation of enone **15**, in which Whitmore reported higher regioselectivity (10:1), albeit in lower yield (75% *vs.* 22% yield).[8] The unsubstituted alkenes **26** and **28** provided different regioselectivity, wherein the major products are **15** in 78% yield (**15**:**27** = 6.8:1) and **29** in 77% yield (**29**:**30**:**31** = 6.5:2.5:1).

Figure 2.3 *Stereoelectronic Stabilisation of Axial Hydrogen Abstraction over Equatorial.*

Corey and Turner independently demonstrated that the prefered hydrogen abstraction is axial over equatorial, due to the favourable stereoelectronic effect from the developing p-orbital mixing with the π-system (Fig. 2.3).[15,16] The high regioselectivity in the allylic oxidation of polycyclic substrates is due to the conformational rigidity. For example, the axial C-6 hydrogen is hindered by the angular C-10 methyl group, which promotes C-3 abstraction (Fig. 2.4). The same argument can also be applied to the flexible, monocyclic examples, where the axial C-4 methyl group protects the C-6 hydrogen, whereas the C-3 hydrogen is not

affected by this 1,3-diaxial interaction. This is highlighted in the alkene **28**, which affords a mixture of enones **29/30/31** (Scheme 2.5).[12]

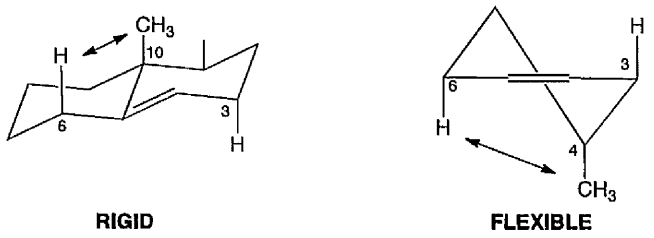
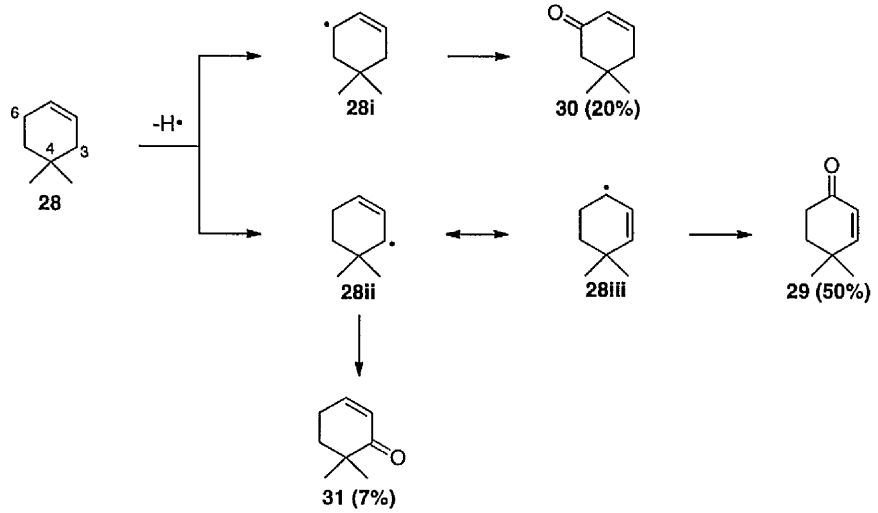


Figure 2.4 *Conformation of Rigid and Flexible Alkenes.*

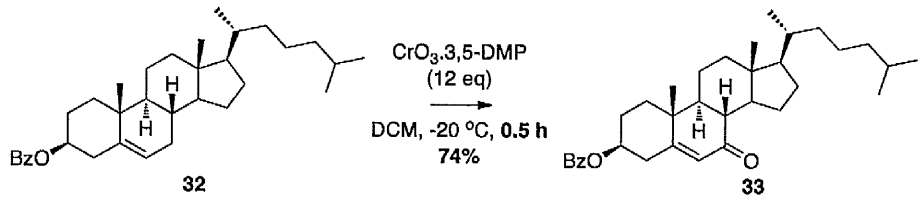
The major enone **29** comes from the abstraction of the C-3 hydrogen to furnish the intermediate **28ii**, followed by isomerisation presumably leading to the more stable allylic radical **28iii** followed by its oxidation to the enone **29** (Scheme 2.5).[17] The enone **31** results from the intermediate **28ii**, which is disfavoured due to the steric hindrance of the *gem*-dimethyl groups. The competing hydrogen abstraction of alkene **28** at C-6 leads to the intermediate **28i**, which is oxidised to afford the enone **30**. The distribution of the enones indicates that the initial abstraction of alkene **28** is 3:1 in favour of the C-3 hydrogen over the C-6 hydrogen, due to the 1,3-diaxial interaction between the axial C-6 hydrogen and C-4 methyl group.[12]



Scheme 2.5 *Product Distribution of Alkene 28.*

In 1978, Salmond discovered that chromium trioxide-3,5-dimethylpyrazole (CrO_3.3,5-DMP) was a superior oxidant compared to Collins reagent for the allylic

oxidation of steroidal alkenes (Scheme 2.6).[18] For instance, the oxidation of cholesterol benzoate **32** is more efficient than related chromium oxidants.[19] This was attributed to improved solubility of the reagent, which promotes intermolecular hydrogen abstraction *via* the increased basicity of the proximal nitrogen in the pyrazole nucleus.[20]



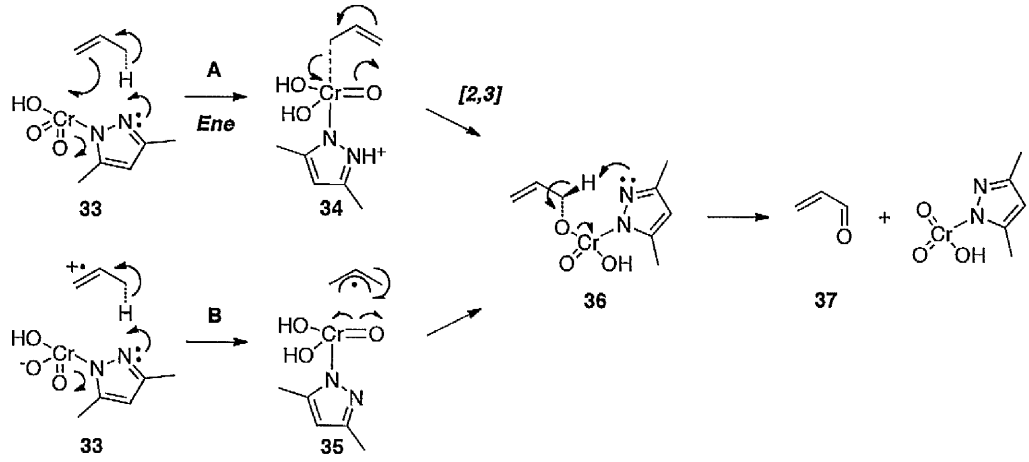
c.f. 1. Sodium chromate, acetic acid/acetic anhydride, **72-96 h, 38%**

2. Collins reagent, DCM, celite, **50 h, 68%**

3. Pyridinium chlorochromate, DCM, **N.R.**

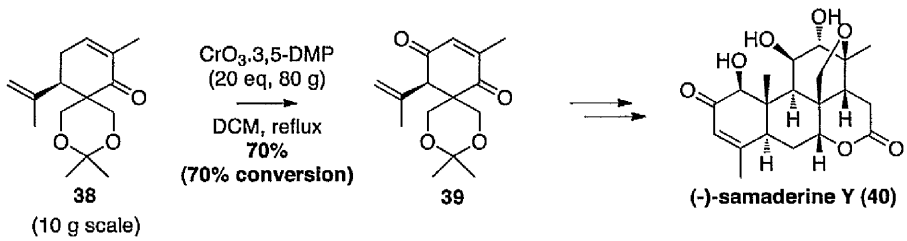
Scheme 2.6 *Chromium Allylic Oxidations on Cholesterol Benzoate 32.*

Scheme 2.7 outlines the two mechanisms proposed by Salmond for the CrO_3.3,5-DMP allylic oxidation reaction. The first pathway proceeds through an ene-type process with **33** to generate **34**, which then undergoes a sigmatropic [2,3]-rearrangement to furnish the intermediate **36** (Path **A**, Scheme 2.7).[21,22] This pathway is not possible with the Collins reagent as there are no vacant coordination sites for complexation with π-electrons and no basic nitrogen for assisted removal of the allylic hydrogen



Scheme 2.7 *Proposed Mechanisms of CrO_3.3,5-DMP Allylic Oxidations.*

The alternative pathway involves a one-electron oxidation of the double bond by CrO_3.3,5-DMP to provide the radical cation, which undergoes a proton abstraction by the pyrazole ligand to furnish the allyl radical **35** (Path **B**, Scheme 2.7).[23] The allyl radical **35** undergoes a further one electron transfer to afford the intermediate **36**, which is the same intermediate formed in path **A**. This intermediate rearranges to provide the *α, β*-unsaturated aldehyde **37** and regenerate the CrO_3.3,5-DMP reagent.[24,25] Hence, the regeneration of the oxidant should enable the oxidation to become catalytic, but CrO_3.3,5-DMP is generally used in large excess. For example, Shing utilised 20 equivalents of CrO_3.3,5-DMP (80 grams) to effect the allylic oxidation of the electron deficient alkene **38** to afford the enone **39** in 70% yield, in the total synthesis of (-)-samaderine Y **40** (Scheme 2.8).[26]



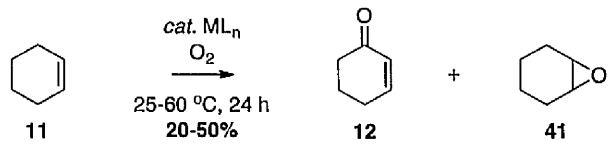
Scheme 2.8 *CrO_3.3,5-DMP Allylic Oxidation in the Total Synthesis of (-)-Samaderine Y **40**.*

2.1.3. Metal-Catalysed Methods

2.1.3.1. Molecular Oxygen as the Terminal Oxidant

The development of metal-catalysed allylic oxidation reactions using environmentally benign reagents namely, molecular oxygen and hydrogen peroxide has been the focus of intense synthetic attention.[27] In 1967, Collman reported the transition metal-catalysed autoxidation of cyclohexene **11** under a atmosphere of molecular oxygen to furnish cyclohexen-3-one **12** in 20-50% yield with cyclohexene oxide **41** as the minor product (Scheme 2.9).[28] The autoxidation proceeds with an array of transition metals, which includes rhodium, platinum and iridium. The

oxidation proceeds through a hydroperoxide intermediate, which has also been reported for the thermal autoxidation of cyclohexene.[29]

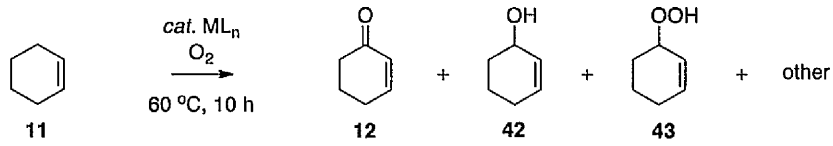


ML_n = $RhCl(CO)(PPh_3)_2$, $PtO_2(PPh_3)_2$, $IrI(CO)(PPh_3)_2$, $IrCl(N_2)(PPh_3)_2$ or $RhCl(PPh_3)_3$

Scheme 2.9 *Transition Metal-Catalysed Autoxidation Reaction by Collman et al.*

In 1968, Kurkov performed the autoxidation of cyclohexene **11** and ethylbenzene, and demonstrated that the reaction proceeds *via* a free-radical chain mechanism (Table 2.1).[30] Both the rhodium and cobalt-catalysed autoxidation reactions occur with similar product mixtures (Table 2.1, entries 1-4).

Table 2.1 *Metal-Catalysed Autoxidation of Cyclohexene **11** by Kurkov et al.*



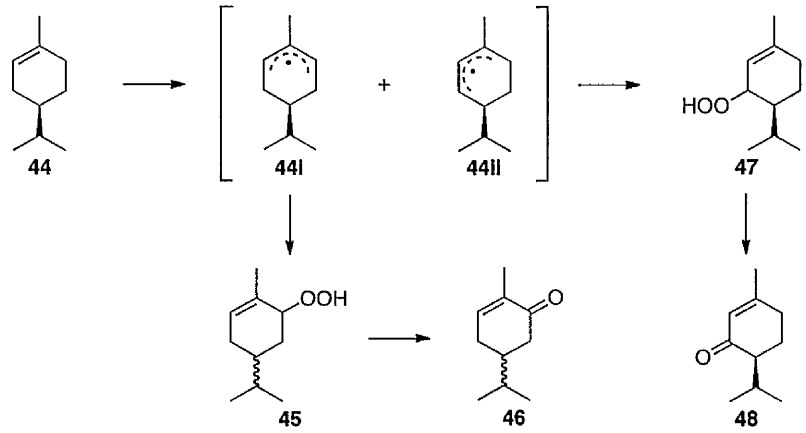
Entry	Catalyst	Conv. (%)	Yield (%)			
			12[a]	42[a]	43[b]	Other[c]
1	$RhCl(PPh_3)_3$	63	35	28	27	14
2	$Rh(acac)_3$	78	51	20	18	11
3	$Rh(2\text{-EH})_3$	62	57	20	15	8
4	$Co(2\text{-EH})_2$	79	48	20	21	11
5[d]	***$RhCl(PPh_3)_3$***	***0***	-	-	-	-
6	None	1	-	-	-	-

[a]Determined by GLPC. [b]Determined iodometrically. [c]Unidentified products. [d]In the presence of 2 mol % of hydroquinone.

A number of additional products were isolated, including the 2-cyclohexen-1-yl hydroperoxide **43**, which was previously proposed as an intermediate in the process. Hydroperoxide **43** was proposed to fragment to the enone **12** and the allylic alcohol **42**. The free-radical nature of the autoxidation reaction was supported by the

observation that there was complete inhibition of the oxidation in the presence of hydroquinone, a free-radical scavenger (entry 5).[30]

In 1969, Baldwin provided additional evidence for the intermediacy of an allyl radical during the allylic oxidation of (+)-carvomenthene **44** (Scheme 2.10).[31] The oxidation of optically active (+)-carvomenthene **44** generates two allyl radical intermediates, prochiral-**44i** and **44ii**, in which the former provided the enone **46** as the racemate and the piperitone product **48** with retention of optical purity.



Scheme 2.10 *Allyl Radical via the Autoxidation of (+)-Carvomenthene 44.*

The Haber-Weiss type mechanism has been proposed for the transition-metal-catalysed free-radical chain reaction based on the following observations.[32] This mechanism can be initiated by many transition metals that can undergo a one-electron transfer, e.g. $Fe^{2+} \rightarrow Fe^{3+}$, $Cu^{1+} \rightarrow Cu^{2+}$, $Co^{2+} \rightarrow Co^{3+}$, $Rh^{2+} \rightarrow Rh^{3+}$, and two-electron transfer, for example, $Sn^{2+} \rightarrow Sn^{4+}$, $Tl^{1+} \rightarrow Tl^{3+}$, $Rh^{1+} \rightarrow Rh^{3+}$, $Cr^{3+} \rightarrow Cr^{5+}$ (Fig 2.5).[33,34]

One-electron transfer

$$ROOH + M(II) \longrightarrow ROO\cdot + H^{+} + M(I)$$

$$ROOH + M(I) \longrightarrow ROH + OH^{-} + M(II)$$

Two-electron transfer

$$2ROOH + M(III) \longrightarrow 2ROO\cdot + 2H^{+} + M(I)$$

$$2ROOH + M(I) \longrightarrow 2RO\cdot + 2OH^{-} + M(III)$$

Figure 2.5 *Haber-Weiss Mechanism of One/Two-Electron Transfer.*

2.1.3.2. Peroxides as the Terminal Oxidant

Robertson, Waters and Medvedev reported the transition metal decomposition of hydroperoxides to RO• and ROO•.[35-37] For instance, they reported that the rate of autoxidation of tetralin **49** with molecular oxygen, without the presence of metal salts afforded approximately 30% yield of **51** and **52** based on hydroperoxide **50** content. However, the rate gradually declined after the "induction period" of phases **A** and **B** (Fig. 2.6).[35] In the presence of metal salts (Cu^{+}, Fe^{2+} or Co^{2+}), phases **A** and **B** can potentially be bypassed, to access the tetralol **51**, tetralone **52** and hydroxyl radical **53**. Haber and Weiss demonstrated that hydroperoxides are decomposed with metal salts, especially ones that undergo one-electron transfer, leading to the increased formation of secondary initiators, such as hydroxyl radical **53**.[32] Hence, the role of the metal salts was identified as the "secondary catalyst", to aid the decomposition of the initially formed hydroperoxide **50** to generate the "active catalyst".[38,39]

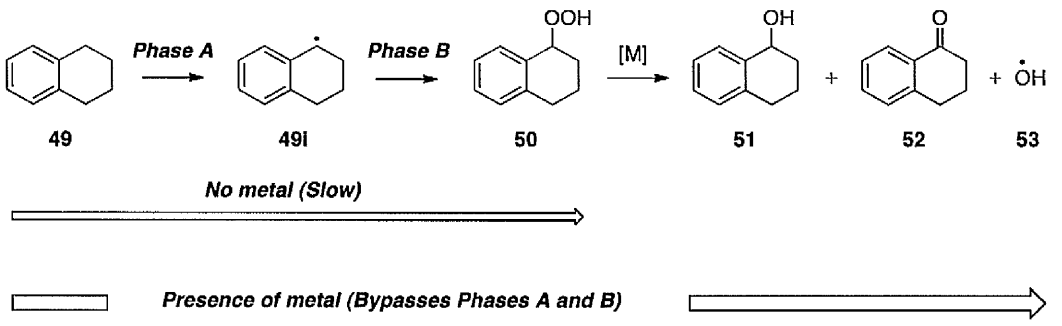
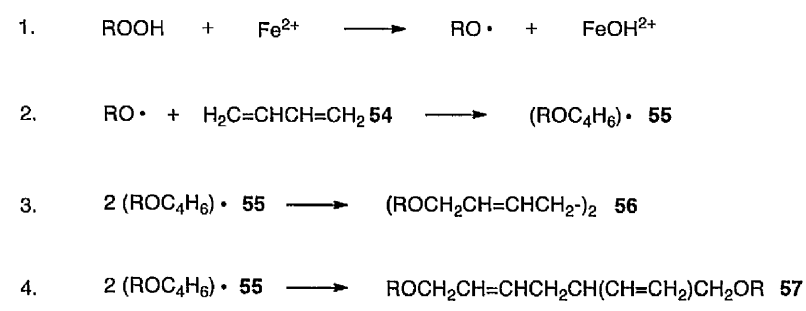


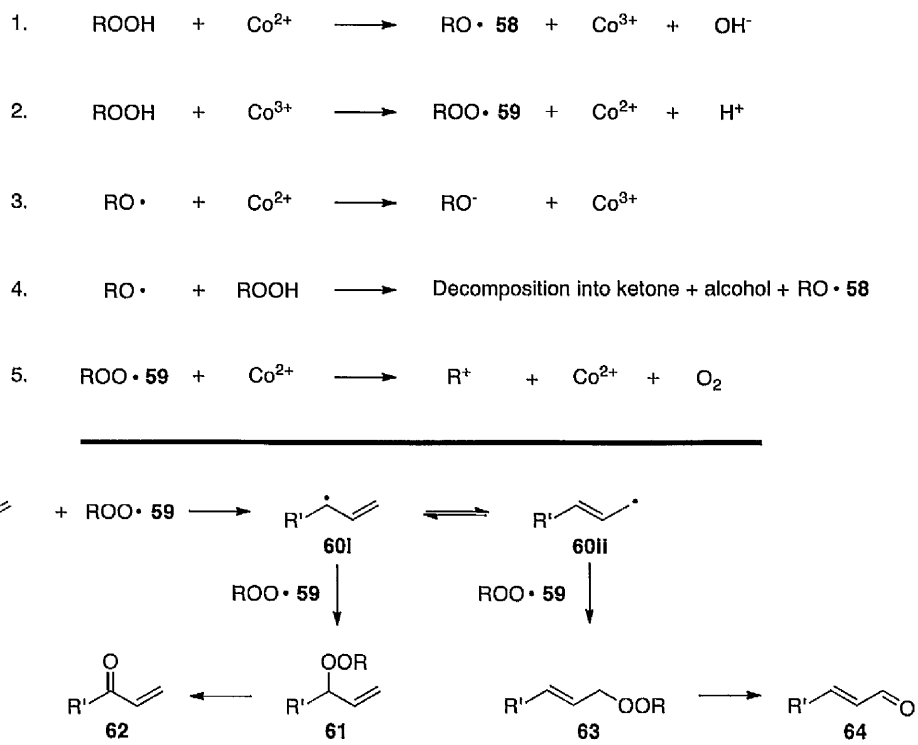
Figure 2.6 *Effect of Metal Salt on the Rate of Autoxidation of Tetralin 49.*

In 1951, Nudenberg investigated the free-radical decomposition of a range of alkyl hydroperoxides (Scheme 2.11).[40] Alkyl peroxides were exposed to ferrous ammonium sulphate hexahydrate in the presence of butadiene **54**, underwent decomposition to give the corresponding alkoxy radicals.[41] The addition of a hydroxyl radical to butadiene **54** provided the free radical **55**, which dimerised to afford **56** and **57**.[40]



Scheme 2.11 *Addition of Alkoxy Radicals to Conjugated Systems by Nudenberg et al.*

Nudenberg also reported the addition of free radical **59** to acceptors (alkenes), which was initiated by the decomposition of *tert*-butyl hydroperoxide with trace amounts of cobalt salts (Scheme 2.12).[42] The decomposition of *tert*-butyl hydroperoxide proceeds by a chain mechanism to afford the oxygen-centred radicals ROO• **59** and RO• **58**, along with molecular oxygen.[43]



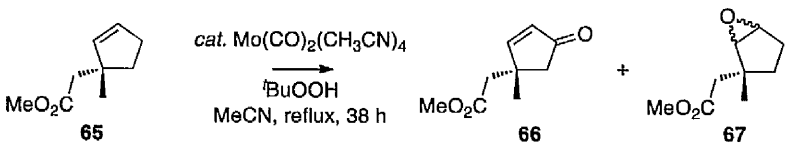
Scheme 2.12 *Addition of Alkoxy Radicals to Alkenes by Nudenberg et al.*

The evolution of oxygen from the decomposition of ROO• **59** by cobalt salts could be suppressed if acceptors of free ROO• **59** radicals were present (Scheme 2.12).[42] For example, in the presence of 1-octene **60**, the free radical **59** affected an allylic hydrogen abstraction reaction to generate the isomeric alkyl radicals **60i** and

60ii, which reacted with ROO• **59** to furnish the enone **62** and aldehyde **64** from the decomposition of the respective peroxides **61** and **63**.[42]

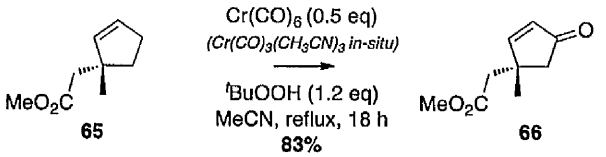
2.1.3.3. Chromium-Catalysed Allylic Oxidations

Significant progress has been made into the allylic oxidation of alkenes using hydroperoxides with transition metal catalysts.[45] For instance, Nudenberg has applied copper, iron and cobalt in the allylic oxidation of several alkenes.[40-43] More recently, catalytic chromium(0) and chromium(III) with *tert*-butyl hydroperoxide have been utilised for allylic oxidation.[4d] Pearson serendipitously discovered that $Mo(CO)_2(CH_3CN)_4$ catalyses the oxidation of cyclopentene **65** to cyclopentenone **66** using *tert*-butyl hydroperoxide (Scheme 2.13).[46]

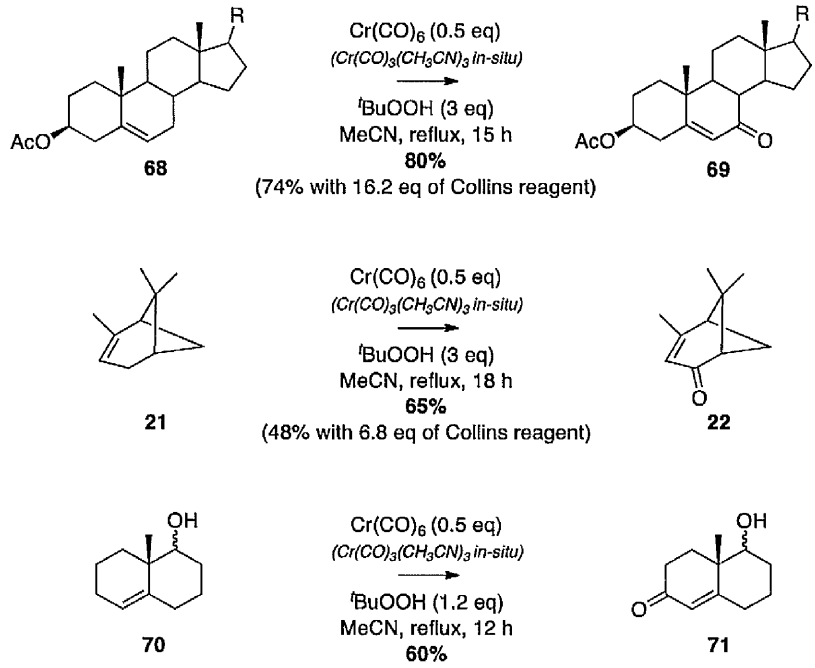


Scheme 2.13 *Allylic Oxidation using Catalytic Molybdenum by Pearson et al.*

Interestingly, chromium-carbonyl catalysts were effective in this transformation, especially when the *in situ* generated $Cr(CO)_3(CH_3CN)_3$ catalyst was employed (Scheme 2.14).[47] Treatment of cyclopentene **65** with $Cr(CO)_6$ in refluxing acetonitrile to generate the $Cr(CO)_3(CH_3CN)_3$ complex afforded the cyclopentenone **66** exclusively in 83% yield (Scheme 2.14). Although it was feasible to utilise catalytic quantities of $Cr(CO)_6$ (5 mol %), sub-stoichiometric quantities (0.5 eq) were required to provide a good rate of reaction and prevent the formation of the side products (Scheme 2.14).[46]

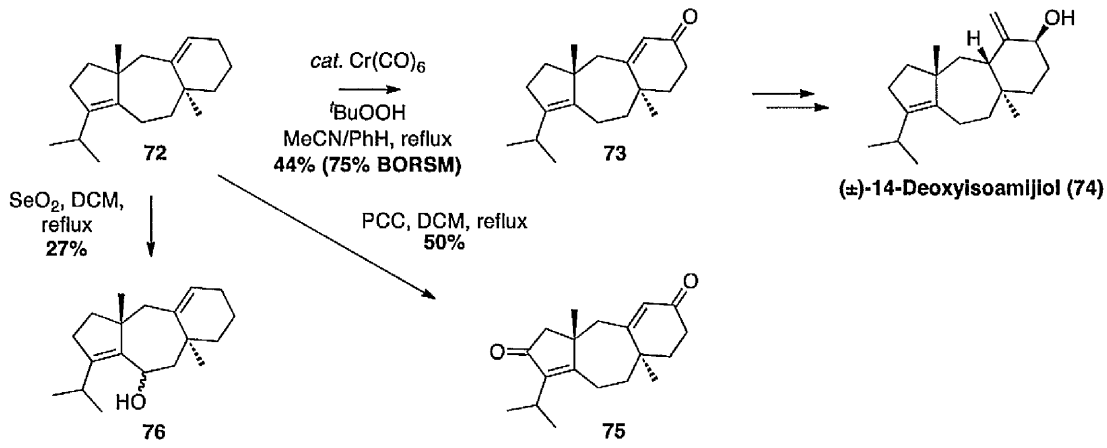


Scheme 2.14 *Allylic Oxidation using Catalytic Chromium by Pearson et al.*



Scheme 2.15 *$Cr(CO)_6$-Catalysed Allylic Oxidation.*

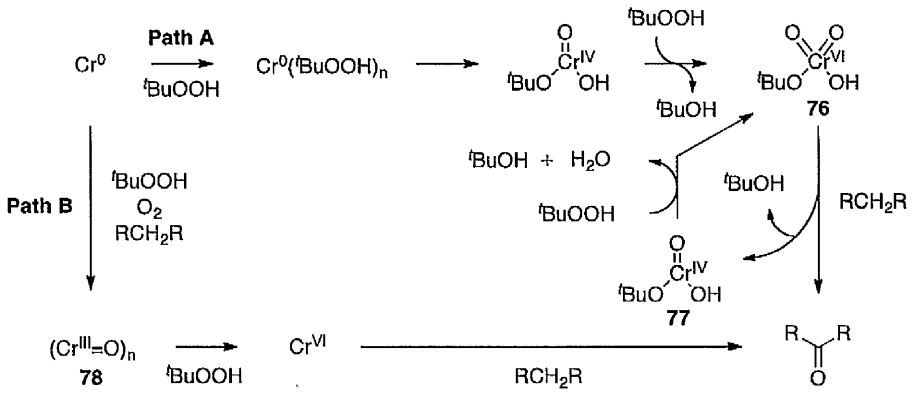
The chromium-catalysed allylic oxidation reaction was superior to the previous methods, as demonstrated by the substrate scope (Scheme 2.15).[12] The oxidation reaction provided excellent chemoselectivity, as exemplified by the oxidation of alcohol **70** to provide the enone **71** without competitive oxidation of the secondary alcohol.[4c]



Scheme 2.16 *Pearson's Conditions Towards the Total Synthesis of (±)-14-Deoxyisoamijiol 74.*

The chromium-catalysed allylic oxidation reaction was also used in the total synthesis of (±)-14-deoxyisoamijiol **74** (Scheme 2.16).[48] Treatment of the alkene **72** with catalytic $Cr(CO)_6$ and *tert*-butyl hydroperoxide afforded the enone **73** in 44% yield (75% BORSM) with the chemoselective oxidation of the cyclohexene over the cyclopentene. Interestingly, the oxidation of **72** with more conventional oxidants provided the over-oxidised product **75** and the allylic alcohol **76**.[49]

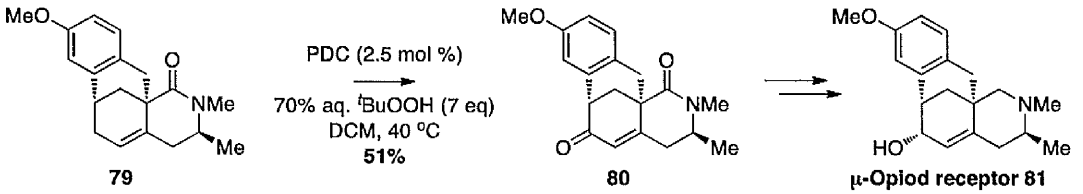
The mechanism for the chromium-catalysed oxidation reaction has been explored, in which two possible pathways have been proposed (Scheme 2.17). The first pathway involves the oxidation of chromium(0) to the active chromium(VI) species **76** by *tert*-butyl hydroperoxide (Scheme 2.17, Path **A**).[50] The oxidation of the alkane with **76** leads to the desired carbonyl product and the chromium(IV) species **77** which regenerates **76** with *tert*-butyl hydroperoxide. The second pathway involves the formation of polymeric chromium(III) oxide **78** and a chromium(VI) species (Scheme 2.17, Path **B**). The former **78** is known to possess superior catalytic activity compared to $Cr(CO)_6$.[50] Chromium(III)-catalysed allylic oxidations have not been examined extensively and many of the earlier conditions employ mixed-metal systems, e.g. MCr_2O_4 (where M = Co, Cu, Ni)] and molecular oxygen.[51]



Scheme 2.17 *Proposed Mechanism for the Active Chromium Catalyst.*

Schultz utilised pyridinium dichromate (PDC) for an allylic oxidation in the synthesis of the μ-opiod receptor **81** (Scheme 2.18).[52] Treatment of **79** with catalytic

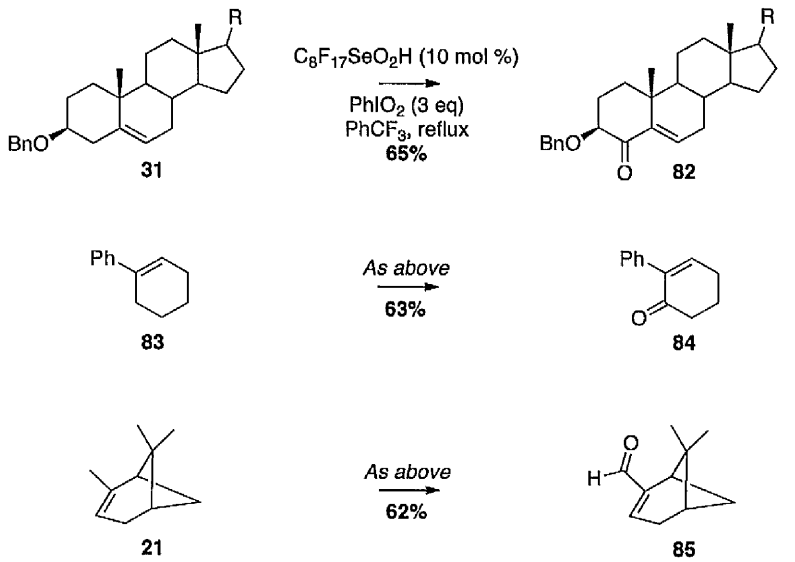
PDC and aqueous 70% *tert*-butyl hydroperoxide furnished the enone **80** in 51% yield. The conditions are exceptionally mild with low catalyst loading (2.5 mol %) using cheap and readily available aqueous *tert*-butyl hydroperoxide.



Scheme 2.18 *PDC-catalysed Allylic Oxidation In the Synthesis of the μ-Opiod Receptor **81**.*

2.1.3.4. Selenium-Catalysed Allylic Oxidations

In 2004, Crich reported the use of a recyclable selenium catalyst for allylic oxidation, which provided similar regioselectivity to the analogous stoichiometric selenium(IV) oxidations (Scheme 2.19).[53] Treatment of the cholesteryl benzoate **31** with $C_8F_{17}SeO_2H$ (10 mol %) and $PhIO_2$ (3 eq) furnished the enone **82** in 65% yield with 92% recovery of the fluorous selenium catalyst.

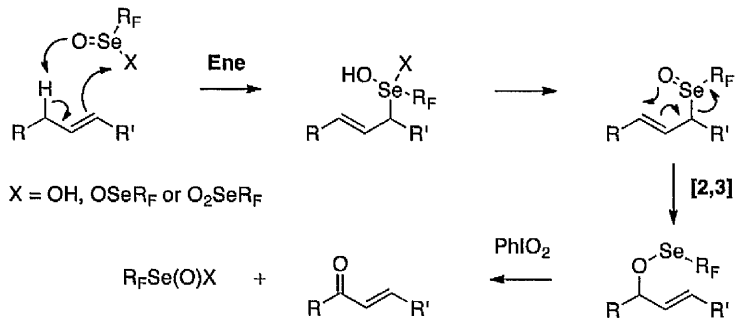


Scheme 2.19 *Selenium-Catalysed Allylic Oxidation.*

The allylic oxidation follows Guillemonat's rules for regioselectivity, which nicely complements the selectivity outlined in previous investigations.[54] Treatment

of the alkenes **83** and **21** with the selenium catalyst in the presence of the oxidant provided the enone **84** and aldehyde **85** in good yield and with excellent regioselectivity (Scheme 2.19). Selenium based oxidation reactions are inherently problematic due to high toxicity and waste disposal issues, but nevertheless, this catalytic variant provides an interesting alternative.[55]

Crich proposed that the catalytic selenium oxidation with $PhIO_2$ proceeds as outlined in Scheme 2.20, which parallels the mechanism of selenium dioxide oxidation reactions. Hence, the process involves an initial ene reaction, followed by a [2,3]-sigmatropic arrangement to the selenic ester, which is then eliminated to provide the carbonyl functionality.[56]



Scheme 2.20 *Proposed Mechanism for the Selenium-Catalysed Allylic Oxidation.*

2.1.3.5. Iron-Catalysed Allylic Oxidations

Barton *et al.* demonstrated the iron-catalysed allylic oxidation reactions on terpenes, using Gif systems.[57] It was presumed that the Gif chemistry replicated nature's aerobic system by the oxidation of iron(0) to iron(III). The chemistry was originally developed for the oxidation of saturated hydrocarbon systems *via* the *in situ* formation of iron(V) oxide using various Gif systems developed by Barton (Fig. 2.7).[58]

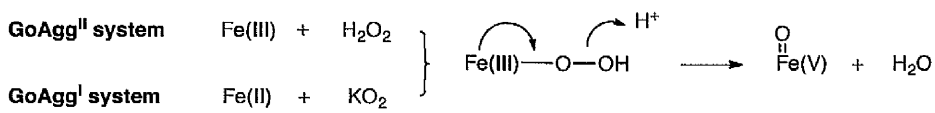
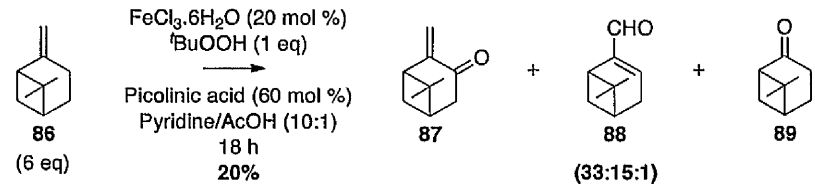


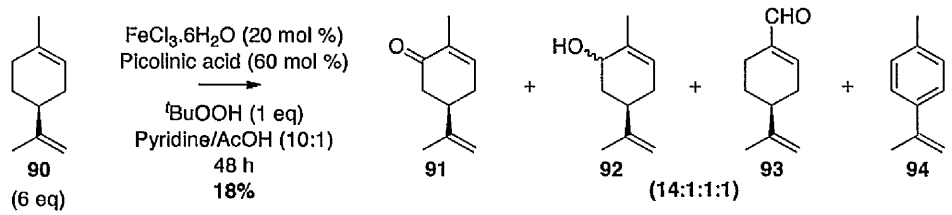
Figure 2.7 *Gif Chemistry.*

The Gif chemistry was applied to the allylic oxidation of β-(-)-pinene **86** and *R*-(+)-limonene **90** using Fe(III)-TBHP and Fe(III)-TBHP-PA conditions under aerobic atmosphere.[59] Treatment of β-(-)-pinene **86** with $FeCl_3.6H_2O$, *tert*-butyl hydroperoxide and picolinic acid in pyridine/acetic acid furnished the pinocarvone **87**, myrtenal **88** and nopinone **89** in low yield with modest selectivity (Scheme 2.21). The oxidation required air; since the yield was significantly reduced under an atmosphere of argon with moderate increase in yields over prolonged reaction times.[59,60]



Scheme 2.21 *Iron(III)-Catalysed Allylic Oxidation of β-(-)-Pinene 86.*

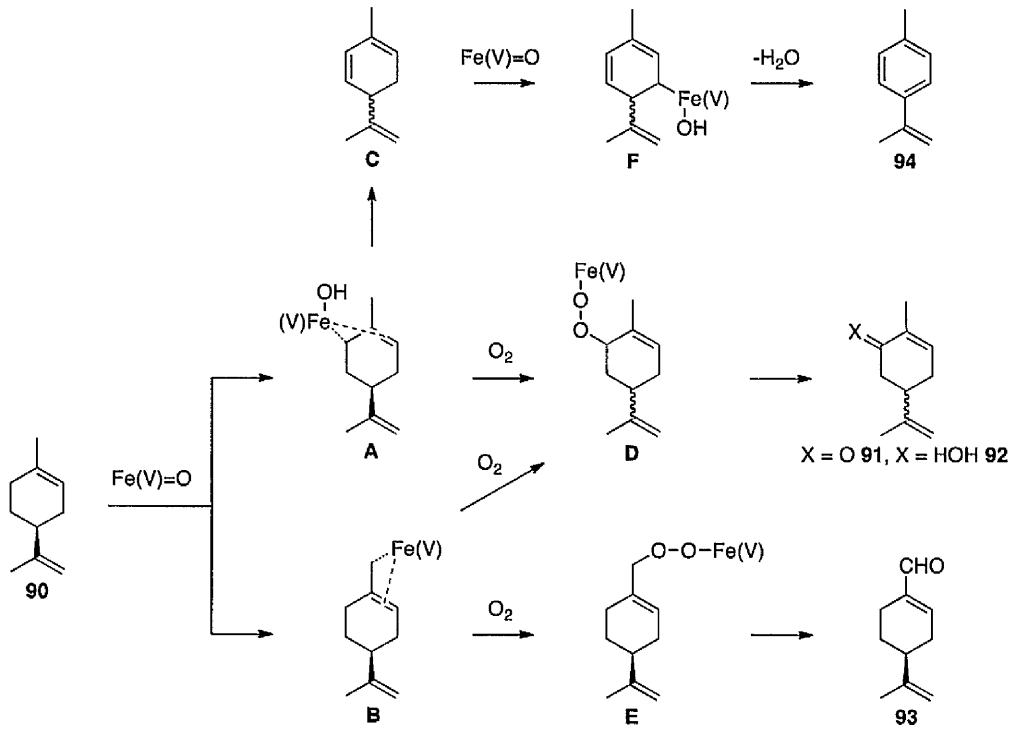
Alternatively, treatment of *R*-(+)-limonene **90** with the catalytic iron(III) provided mixtures of carvone **91**, carveol **92**, perillaldehyde **93** and 4-(2-propenyl)toluene **94** (Scheme 2.22).[59] The oxidation was dependent on picolinic acid (PA) and air, but the selectivities and yields are modest.



Scheme 2.22 *Iron(III)-Catalysed Allylic Oxidation of R-(+)-Limonene 90.*

The proposed mechanism for the iron(III)-catalysed allylic oxidation of *R*-(+)-Limonene **90** is outlined in Scheme 2.23. The anticipated Fe(V)=O species reacts with either the secondary or primary allylic C-H bond to afford the intermediates **A** and **B**.[61] The reaction of **A** (at both the α- and γ-carbon) with molecular oxygen provides the racemic intermediate **D**. Carvone **91** and carveol **92** are derived from the decomposition of **D**, whereas perillaldehyde **93** is derived from the fragmentation of

the primary allylic metal hydroperoxide **E**. Intermediate **A** can also undergo elimination to provide the cyclohexadiene **C**, which reacts with Fe(V)=O to furnish **F** that can readily rearomatise to 4-(2-propenyl)toluene **94**.[60]

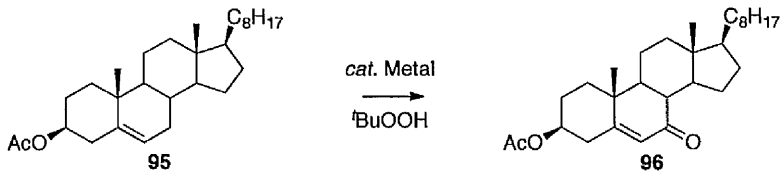


Scheme 2.23 *Proposed Mechanism for the Iron(III)-Catalysed Allylic Oxidation of R-(+)-Limonene* ***90****.*

2.1.3.6. Metal-Catalysed Allylic Oxidations of Δ^5-Steroids

The allylic oxidation of steroids has attracted a great deal of attention, which can be attributed to the necessity to derivatise these bioactive intermediates to elicit a new biological response. For example, the oxidation of Δ^5-steroids to the corresponding 5-en-7-ones inhibit the enzymatic conversion of dihydrolanosterol into cholesterol.[63] Many metal catalysts have been employed with *tert*-butyl hydroperoxide to prepare these allylic oxidation products from Δ^5-steroids in good yield (Table 2.2).[64]

Table 2.2 *Metal-Catalysed Allylic Oxidation of Cholesteryl Acetate* ***95****.*

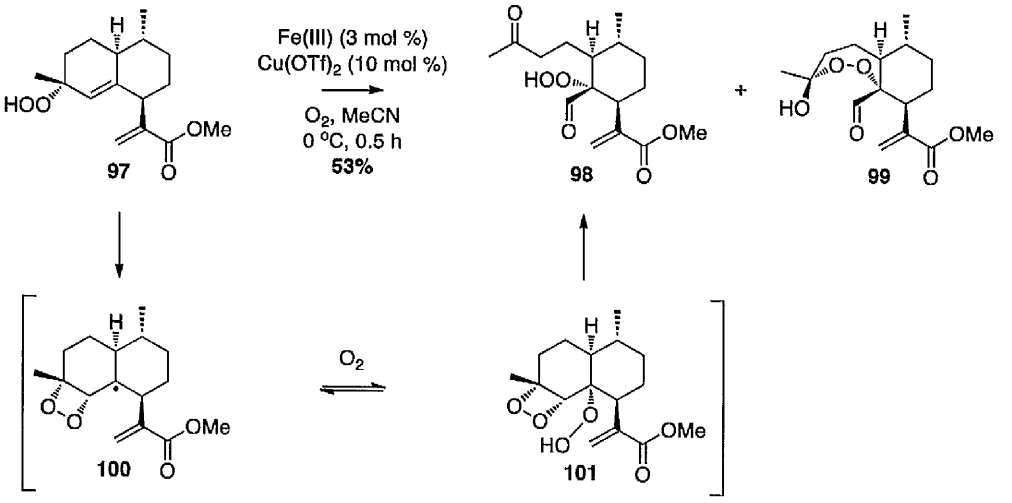


Entry	Catalyst (mol %)	^{t}BuOOH (eq)	Solvent	Temp (^{o}C)	Time (h)	Yield (%)
1	$Fe(acac)_3$ (9)	19.5	Benzene	85	24	74
2	$RuCl_3$ (0.7)	10	Cyclohexane	20	24	75
3	$BiCl_3$ (10)	10	Acetonitrile	70	20	88
4	CoPPS2 (0.048)	6	Benzene	70	20	80

Treatment of cholesteryl acetate **95** with tris(acetylacetonato)iron(III) (9 mol %) and *tert*-butyl hydroperoxide afforded the corresponding enone **96** in 74% yield, albeit using 19.5 equivalents of *tert*-butyl hydroperoxide (Table 2.2, entry 1).[65] Salvador has reported the catalytic bismuth oxidation of **95** to furnish **96** in 88% yield (entry 3),[66] whereas Miller and coworkers at Merck have described the catalytic ruthenium oxidation of **95** with catalytic quantities of $RuCl_3$ (0.7 mol %) to generate **96** in 75% yield (entry 2).[67] Finally, Jurado-Gonzalez developed a cobalt(II) phosphonate modified silica oxidation to afford **96** in 80% yield (entry 4).[68]

2.1.3.7. Copper-Catalysed Allylic Oxidations

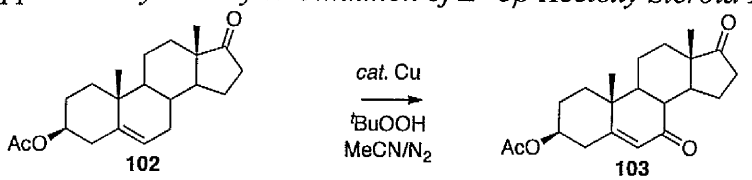
Robertson and Waters reported the copper-catalysed allylic oxidation using copper salts to assist the decomposition of hydroperoxides *via* Haber-Weiss process.[35] In 1990, Haynes expanded this process with the decomposition of the hydroperoxide **97** using $Cu(OTf)_2$, co-catalysed with $Fe(phenanthroline)_3(PF_6)_3$. The addition of the hydroperoxide-radical to the alkene furnished a mixture of the dicarbonyl hydroperoxide **98** and peroxy hemiacetal **99** in 53% overall yield (Scheme 2.24).[69]



Scheme 2.24 *Copper-Catalysed Decomposition of Hydroperoxide 97 Towards The Syntheses of Artemisitene and Artemisinin.*

The copper catalyst promotes homolytic cleavage of the hydroperoxide **97** to provide the dioxetanyl alkyl radical intermediate **100** (Scheme 2.24). The alkyl radical **100** is trapped by dioxygen to give the dioxetane hydroperoxide **101**, which is cleaved to provide the dicarbonyl hydroperoxide **98**. Interestingly, the iron catalysis was ineffective in the absence of the copper salt, which may be attributed to the competing reduction of **100** by iron(II) to generate undesired products.[70]

Table 2.3 *Copper-Catalysed Allylic Oxidation of Δ^5-3β-Acetoxy Steroid 102.*



Entry	Catalyst (mol %)	^{t}BuOOH (eq)	Temp (^{o}C)	Time (h)	Yield (%)
1	***CuI (1)***	***6***	***50***	***20***	***83***
2[a]	CuBr (2)	6	55	24	80
3[a]	CuCl (1.5)	6	55	18	81
4[a]	$CuCl_2$ (2)	6	55	24	81
5	Cu (3)	5	50	16	84

[a]**By-products detected by TLC but not detectable in ^{1}H-NMR spectrum**

In 1997, Salvador *et al.* reported the copper-catalysed allylic oxidation of the Δ^5-3β-acetoxy steroid **102** with *tert*-butyl hydroperoxide to afford **103** in up to 84% yield (Table 2.3).[71] Treatment of the Δ^5-3β-acetoxy steroid **102** with a range of copper catalysts in the presence of *tert*-butyl hydroperoxide afforded the enone product **103** in high yields.[71] Acetonitrile was the optimal solvent, since it allowed the oxidation to proceed under lower temperatures and catalyst loading. The optimal results were obtained using copper(I) iodide and copper powder, which furnished **103** in 83% and 84% yield, respectively (Table 2.3, entries 1 and 5). The copper-catalysed allylic oxidation protocol exhibited similar reactivity to the previously developed methods for the oxidation of Δ^5-steroids, albeit that the reaction was cheap and environmentally benign.

Limited progress has been made in copper-catalysed allylic oxidation reactions; however, the development of a recyclable surface functionalised silica-supported copper catalyst **104** is particularly pertinent (Fig. 2.8). The silica-supported catalyst **104** has similar efficiency as the non-supported catalyst, but can be reused in subsequent oxidation reactions.[72]

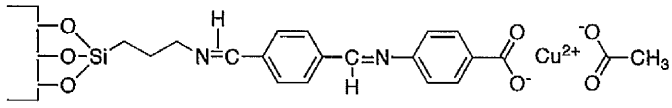
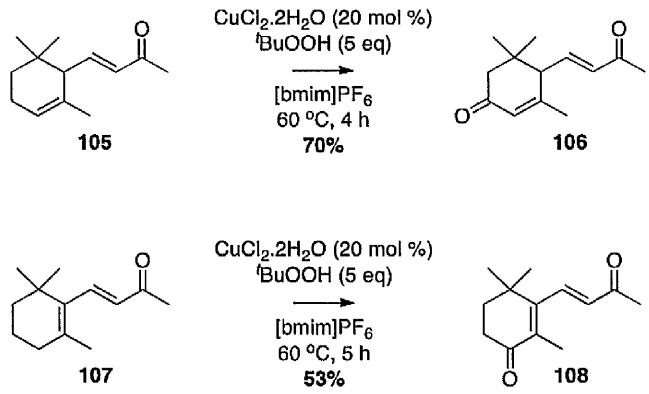


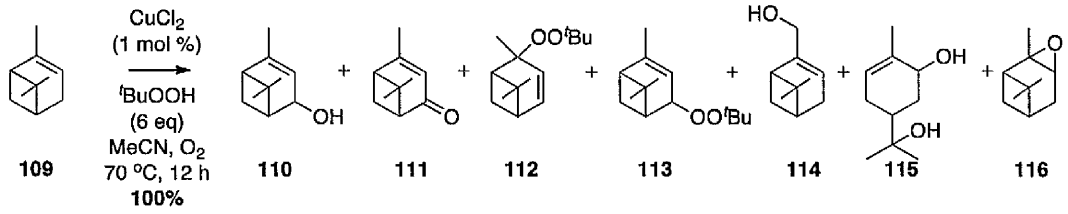
Figure 2.8 *Silica-Supported Copper Catalyst **104**.*

The copper-catalysed allylic oxidation reaction has also been conducted in ionic liquids (Scheme 2.25).[73] Treatment of the dienes **105** and **107** with copper(II) chloride and *tert*-butyl hydroperoxide in [bmim]PF_6 furnished the enones **106** and **108** in 70% and 53% yield, respectively. The [bmim]PF_6 can be recycled up to 6 times, but additional copper(II) chloride (15 mol %) was added in each cycle making its utility impractical.[74]



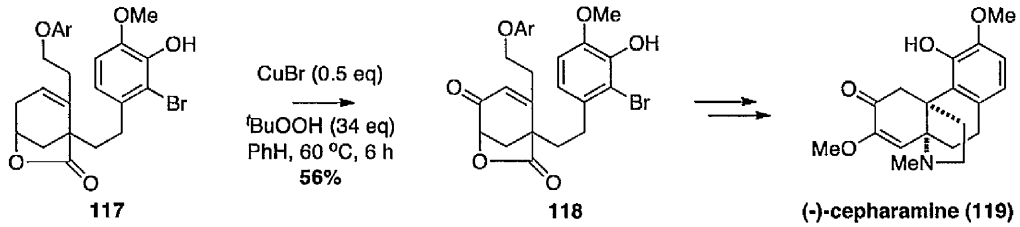
Scheme 2.25 *Combination of Copper-Salt and Ionic Liquid in Allylic Oxidation.*

In 2003, Allal reported the metal-catalysed allylic oxidation of α-pinene **109** with a variety of metal catalysts (Scheme 2.26).[75] The allylic oxidation of α-pinene **109** provided a large mixture of oxidised products with verbenone **111** as the major product. Copper(II) chloride was the optimal catalyst for this transformation, affording the enone **111** in 78% yield (22% of the other isomers). Other metal catalysts were inefficient in this oxidation reaction, generating mixtures of products in poor yield and with low selectivities.[75]



Scheme 2.26 *Metal-Catalysed Allylic Oxidation of α-Pinene **109**.*

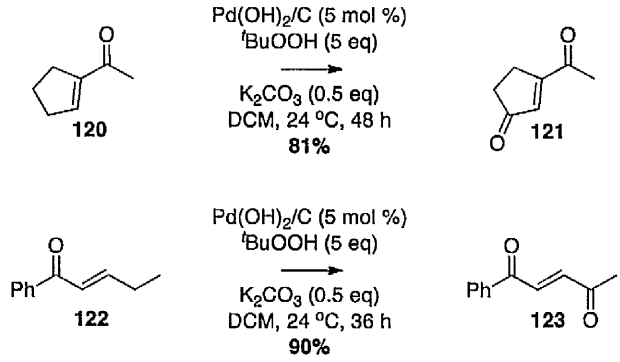
In 1998, Schultz reported the use of a copper-catalysed allylic oxidation reaction in the total synthesis of (-)-cepharamine **119** (Scheme 2.27).[76] Treatment of the lactone **117** with copper(I) bromide and *tert*-butyl hydroperoxide afforded the enone **118** in 56% yield. Nevertheless, the oxidation reaction required sub-stoichiometric copper(I) bromide and a large excess of *tert*-butyl hydroperoxide.



Scheme 2.27 *Copper-Catalysed Allylic Oxidation in the Total Synthesis of (-)-Cepharamine **119**.*

2.1.3.8. Palladium-Catalysed Allylic Oxidations

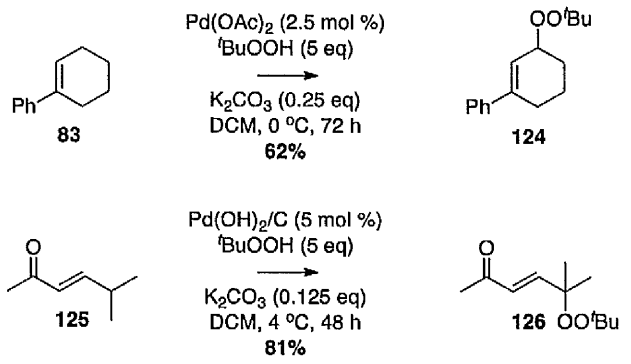
In 2002, Corey and Yu described the palladium-catalysed allylic oxidation of acyclic and cyclic alkenes to generate 1,4-enediones and enones (Scheme 2.28).[77,78] Treatment of 1-acetylcyclopentene **120** with $Pd(OH)_2/C$, potassium carbonate and *tert*-butyl hydroperoxide afforded the enedione **121** in 81% yield after 48 hours.[78] Alternatively, treatment of the acyclic enone **122** under analogous conditions provided the enedione **123** in 90% yield. This protocol provided excellent yields of a variety of 1,4-enediones under mild conditions.



Scheme 2.28 *$Pd(OH)_2/C$-Catalysed Allylic Oxidation by Corey et al.*

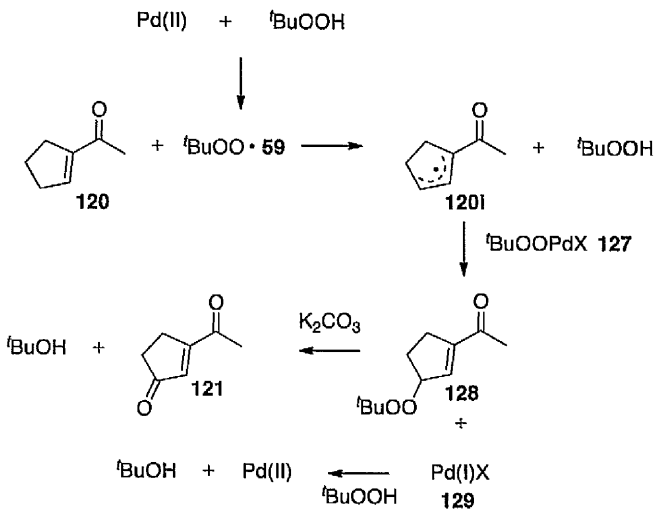
Further studies demonstrated that the 1,4-enediones are formed from the fragmentation of the mixed peroxide intermediate, which was isolated (Scheme 2.29).[79] For example, treatment of 1-phenylcyclohexene **83** with $Pd(OAc)_2$ (2.5 mol %) and potassium carbonate (0.25 eq) afforded the mixed peroxide **124**.[77] Mimoun has reported that palladium(II) carboxylates are converted into $RCO_2Pd(OO^tBu)$ by treatment with *tert*-butyl hydroperoxides, which undergo peroxy palladation of

alkenes.[80] When the substrate has only one γ-hydrogen, for example in enedione **125**, the corresponding *tert*-butylperoxy ether **126** is formed (Scheme 2.29).[78]



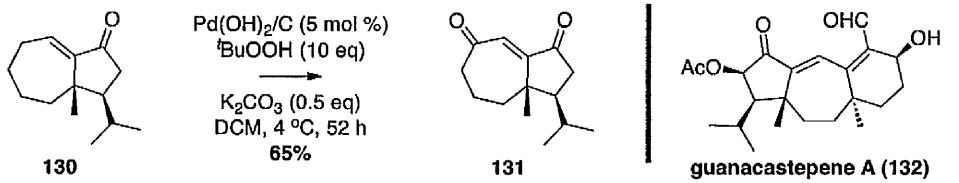
Scheme 2.29 *Pd(OH)$_2$/C -Catalysed Allylic Oxidation to tert-Butylperoxy Ethers.*

The proposed mechanism for the palladium-catalysed allylic oxidation reaction is outlined in Scheme 2.30. Treatment of Pd(II) with *tert*-butyl hydroperoxide generates the ^{t}BuOO• **59** by homolytic cleavage.[69,81] Hydrogen abstraction of alkene **120** with ^{t}BuOO• **59** provides the alkyl radical **120i**, followed by transfer of *tert*-butyl peroxide from **127** to afford the mixed peroxide **128**.[82] *tert*-Butylperoxy ether **128** undergoes the base-catalysed elimination of the mixed peroxide to furnish the enedione **121**.[83,84] The enedione **121** could also arise from the direct capture of **120i** with molecular oxygen, followed by hydroperoxide elimination. Pd(II) is regenerated from the oxidation of Pd(I) **129** with *tert*-butyl hydroperoxide to complete the cycle.[78]



Scheme 2.30 *Proposed Mechanism of the Pd(OH)$_2$/C-Catalysed Allylic Oxidation.*

The $Pd(OH)_2/C$-catalysed allylic oxidation system is relatively general, but the removal of the residual palladium is difficult, making this protocol somewhat tedious.[85] Nonetheless, Chiu and Liu applied the palladium-catalysed allylic oxidation reaction in the synthesis of the core of guanacastepene A **132** (Scheme 2.31).[86] Treatment of the hydroazulenone **130** with $Pd(OH)_2/C$, *tert*-butyl hydroperoxide and potassium carbonate furnished the enedione **131** in 65% yield after 52 hours.[87]



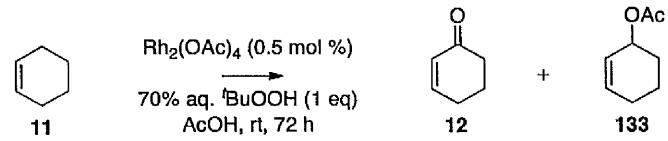
Scheme 2.31 *Palladium-Catalysed Allylic Oxidation Towards the Synthesis of Guanacastepene A* ***132.***

2.1.3.9. Rhodium-Catalysed Allylic Oxidations

Rhodium(I) complexes have previously demonstrated poor activity in the allylic oxidation reactions using molecular oxygen.[28,30] Modest levels of conversion combined with harsh reaction conditions made this procedure impractical. Uemura and Patil reported that cyclohexene **11** undergoes the allylic oxidation in the presence of $Rh_2(OAc)_4$ with 70% aqueous *tert*-butyl hydroperoxide in acetic acid to afford the cyclohexenone **12** and allylic acetate **133** with varying selectivities depending on the stoichiometry of cyclohexene (Scheme 2.32).[79] For example, 1:1 stoichiometry of alkene and oxidant provided 31% yield of **12/133** (9.5:1), whereas a 2:1 stoichiometry, increased the yield and lowered the selectivity (48%, 4.6:1).[79]

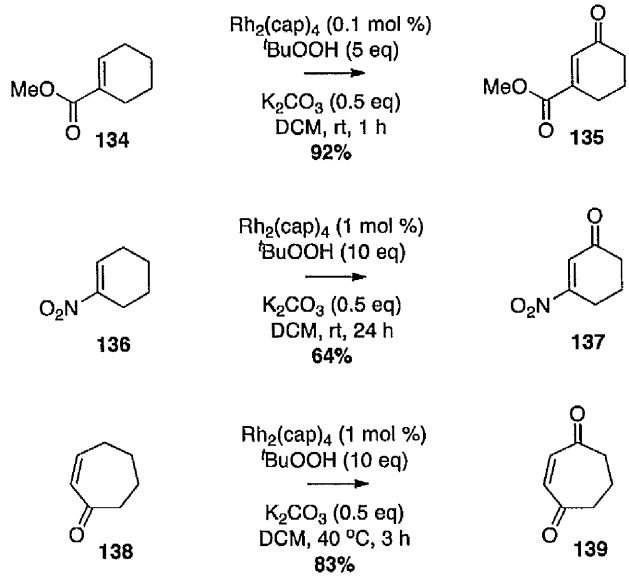
Interestingly, when the oxidation reaction was performed with *tert*-butyl hydroperoxide in the presence of a radical scavenger (6-*tert*-butyl-*o*-cresol or hydroquinone), oxidation was unaffected. However, when molecular oxygen was

used, hydroquinone inhibited the reaction.[30] This suggested that the pathway involving molecular oxygen is free-radical in nature similar to the Rh(I)-catalysed autoxidation, whereas the process involving *tert*-butyl hydroperoxide maybe ionic.



Scheme 2.32 *$Rh_2(OAc)_4$-Catalysed Allylic Oxidation of Cyclohexene **11**.*

In 2004, Doyle *et al.* reported a breakthrough in metal-catalysed allylic oxidation by employing $Rh_2(cap)_4$ with unprecedented activity.[89] The $Rh_2(cap)_4$ catalyst (as low as 0.1 mol %) could perform the allylic oxidations in excellent yield at room temperature (Scheme 2.33).

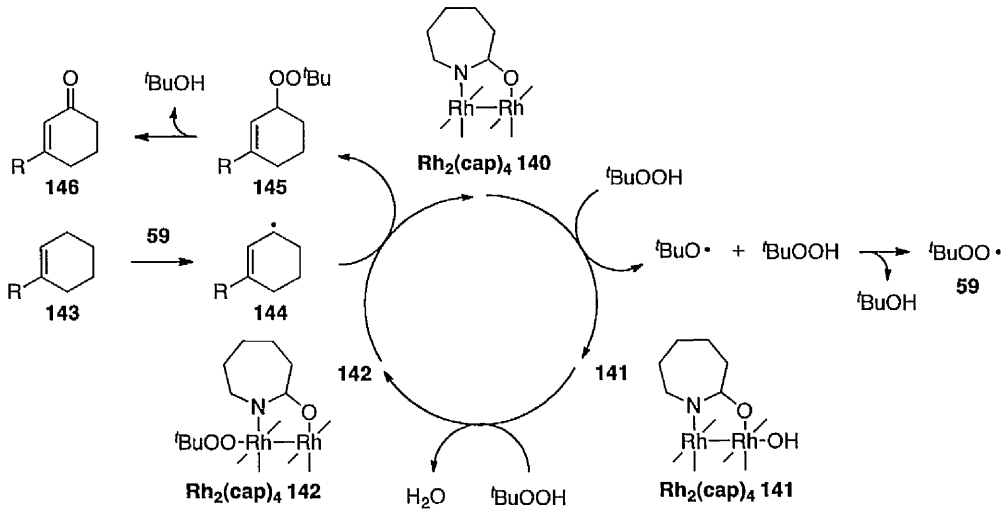


Scheme 2.33 *$Rh_2(cap)_4$-Catalysed Allylic Oxidation by Doyle et al.*

The enhanced catalytic activity was particularly beneficial for the efficient oxidation of electron-poor alkenes, which are not reactive generally (Scheme 2.33). For example, treatment of 1-nitrocyclohexene **136** with $Rh_2(cap)_4$ (1 mol %), potassium carbonate and *tert*-butyl hydroperoxide afforded the enone **137** in 64% yield.[89]

The explanation behind the catalytic activity of $Rh_2(cap)_4$ is the ability of the metal to undergo a 1-electron oxidation.[90] Doyle reported that $Rh_2(cap)_4$ undergoes a reversible oxidation at 55 mV *via* cyclic voltammetry, which corresponds to a Rh_2^{4+} < > Rh_2^{5+} redox couple.[91] The ability of $Rh_2(cap)_4$ to undergo a 1-electron oxidation ($E_{1/2}$ = 11 mV), compared to $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$ ($E_{1/2}$ = 1170 mV and >1800 mV, respectively) is remarkable.[92] The low $E_{1/2}$ is due to the increased electron density of $Rh_2(cap)_4$ as compared to the other Rh(II) complexes, suggests that it can access the Rh_2^{5+} oxidation state more readily.[91]

The proposed mechanism for the $Rh_2(cap)_4$ catalysed allylic oxidation reaction is thought to involve a 1-electron oxidation of **140** with *tert*-butyl hydroperoxide to furnish the *tert*-butyl peroxy radical **59** and the tentatively assigned Rh_2^{5+} species **141** (Scheme 2.34).[69,81] Species **141** is converted to the dirhodium peroxyether complex **142** under the reaction conditions, which is evident by the colour change from light blue to deep red in dichloromethane. The evidence for the generation of the intermediate **142** comes from the UV-visible spectrum of the catalyst after addition of *tert*-butyl hydroperoxide. The data revealed a low-energy adsorption at 974 nm (δ-δ* transitions), which is consistent with a mixed-valent dinuclear metal species.[93] The dirhodium peroxyether complex **142** was isolated as a deep red solid, but efforts to obtain a crystal structure of the complex have been unsuccessful.[89] *tert*-Butyl peroxy radical **59** undergoes the selective hydrogen abstraction of alkene **143** to afford the allylic radical **144**.[94] The recombination of the rhodium peroxide with the allylic radical **144** provides the *tert*-butyl peroxyether **145** and regenerates the Rh_2^{4+} catalyst to complete the cycle.[95] Decomposition of **145** leads to the enone **146** *via* proposed mechanism previously outlined.[83,84] The presence of potassium carbonate was important, since yields were lower in its absence.[83]



Scheme 2.34 *Proposed Mechanism for $Rh_2(cap)_4$-Catalysed Allylic Oxidation.*

The $Rh_2(cap)_4$-catalysed allylic oxidation protocol is superior to the previously reported metal systems, however it utilises the most expensive transition metal (Fig. 2.9).[96] The synthesis and purification of $Rh_2(cap)_4$ is also not trivial, which mandates the development of a more cost effective alternative.[90]

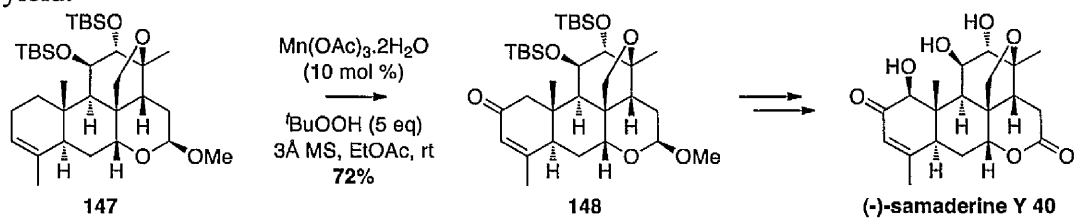
Mn ($0.1/oz) < Zn ($1/oz) < Cu ($4/oz) < Ni ($12/oz) < Ag ($46/oz)

<< Pd ($754/oz) << Au ($1507/oz) < Pt ($1812/oz) < Rh ($2225/oz)

Figure 2.9 *Current Prices of Precious Metals.*

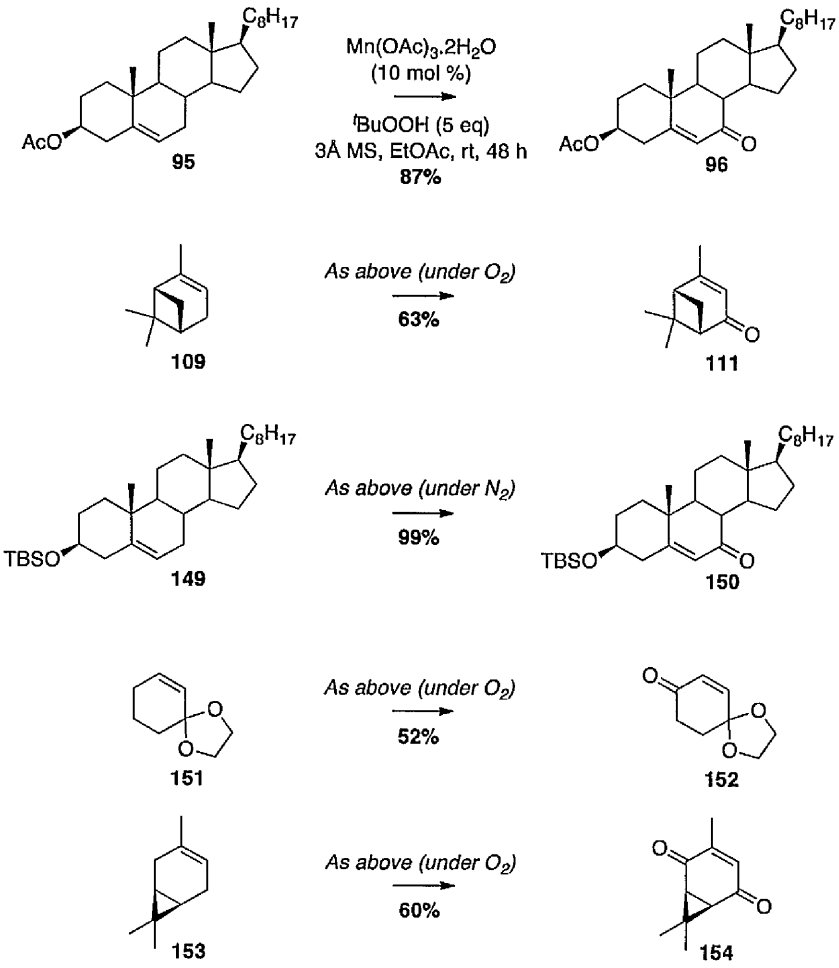
2.1.3.10. Manganese-Catalysed Allylic Oxidations

In 2005, Shing reported the manganese-catalysed allylic oxidation in the total synthesis of (-)-samaderine Y **40** (Scheme 2.35).[26] Treatment of the alkene **147** with $Mn(OAc)_3.2H_2O$ and *tert*-butyl hydroperoxide afforded the enone **148** in 72% yield.[26]



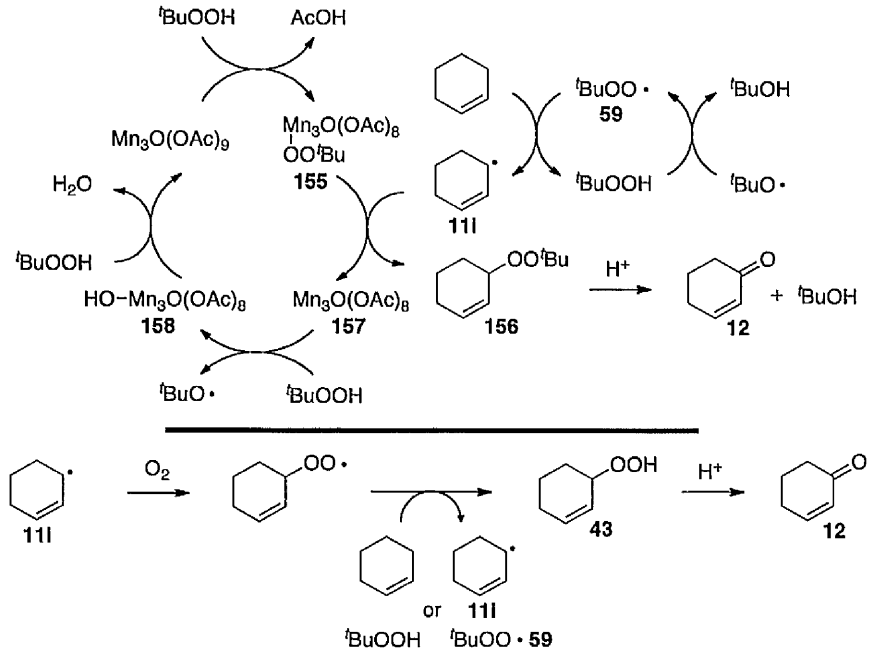
Scheme 2.35 *$Mn(OAc)_3.2H_2O$-Catalysed Allylic Oxidation in the Total Synthesis of (-)-Samaderine Y **40**.*

In 2006, Shing also described the manganese-catalysed allylic oxidation of several Δ^5-steroids and simple alkenes in good yield using anhydrous *tert*-butyl peroxide (Scheme 2.36).[97] Treatment of cholesteryl acetate **95** and silyl ether **149** with $Mn(OAc)_3.2H_2O$ and *tert*-butyl hydroperoxide provided the enones **96** and **150** in 87% and 99% yield, respectively. Treatment of pinene **109** under the modified standard conditions afforded the enone **111** in 63% yield, whilst the ketal **151** furnished the enone **152** in 52% yield.[78,89] Interestingly, (+)-3-carene **153** afforded the over-oxidised enedione **154** instead of the enone. Molecular sieves (3Å) were an essential additive to remove water from the resulting decomposition of the *tert*-butyl hydroperoxide, since the water promotes the disproportionation of $Mn(OAc)_3$.[98]



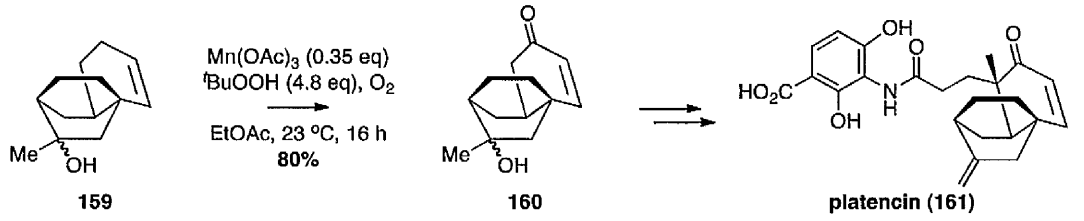
Scheme 2.36 *$Mn(OAc)_3.2H_2O$-Catalysed Allylic Oxidation by Shing et al.*

The proposed mechanism for manganese-catalysed allylic oxidation is similar to the palladium-catalysed mechanism (Scheme 2.37).[78] $Mn_3(OAc)_9$ [$Mn(OAc)_3$ as its trinuclear complex] undergoes the loss of AcOH to afford the complex **155**.[97] Transfer of $^tBuOO\bullet$ **59** to the alkyl radical **11i** provides the mixed peroxide **156** and the manganese complex **157**. Complex **155** is regenerated from the series of reactions of **157** and **158** with *tert*-butyl hydroperoxide. Alternatively, **11i** can react with molecular oxygen to generate the hydroperoxide **43**, followed by decomposition to afford the enone **12**. The mixed peroxide **156** is assumed to decompose under the acidic conditions to give the enone **12**.[97]



Scheme 2.37 *Proposed Mechanism for $Mn(OAc)_3.2H_2O$-Catalysed Allylic Oxidation.*

The $Mn(OAc)_3$-catalysed allylic oxidation reaction was utilised in the late stages of the asymmetric total synthesis of platencin **161**.[99] Treatment of the alkene **159** with $Mn(OAc)_3$ and *tert*-butyl hydroperoxide under an oxygen atmosphere afforded the enone **160** in 80% yield (Scheme 2.38). The manganese-catalysed allylic oxidation protocol was impressive and proves to be a valuable alternative to the palladium- and rhodium-catalysed variants due to the lower cost of manganese.[97]



Scheme 2.38 *$Mn(OAc)_3$-Catalysed Allylic Oxidation in the Total Synthesis of Platencin **161**.*

2.1.4. Regioselectivity in Allylic Oxidations

The ability to control regioselectivity in allylic oxidation reactions has proven particularly problematic, especially with flexible cycloalkenes.[12] For instance, the substrate for these oxidations is generally a tri-substituted cycloalkene, to provide a steric bias for allylic hydrogen abstraction.[78,89,97]

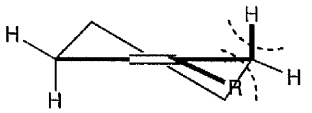
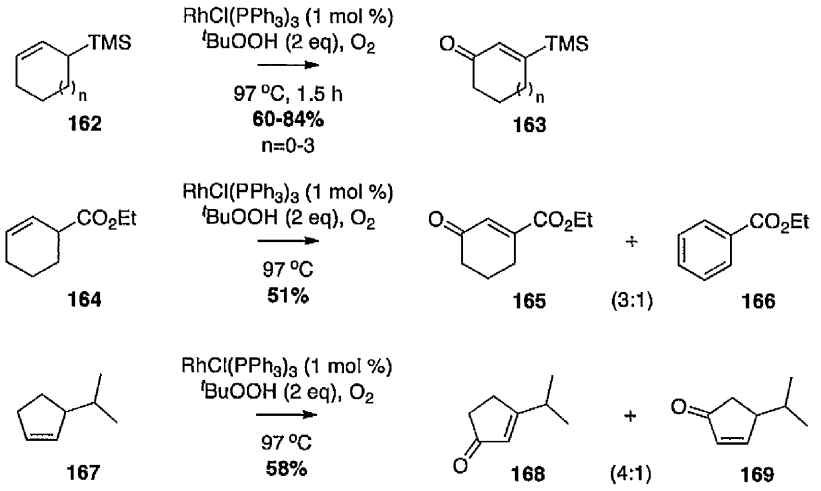


Figure 2.10 *Conformation of Tri-substituted Alkenes.*

In 1978, Salomon reported the rhodium-catalysed autoxidation reaction of allylic trimethylsilyl-, carboethyoxyl- and isopropyl-substituted cycloalkenes **162**, **164** and **167** (Scheme 2.39).[100] Treatment of the 3-(trimethylsilyl)cycloalkenes **162** (where n = 0-3) with $RhCl(PPh_3)_3$ and *tert*-butyl hydroperoxide at 97 °C furnished the isomeric enone **163** in 60-84% yield as a single regioisomer.[100] Ethyl cyclohex-2-enecarboxylate **164** was oxidised under the same conditions to provide a mixture of the isomeric enedione **165** and ethyl benzoate **166**. Finally, the oxidation of 3-isopropylcyclopent-1-ene **167** resulted in a mixture of the isomeric 3-isopropylcyclopent-2-en-1-one **168** and 4-isopropylcyclopent-2-en-1-one **169** in 58% conversion. The failure to control regioselectivity is attributed to the isopropyl group failing to promote allylic C-H bond cleavage in an analogous manner to the carboethoxyl or trimethylsilyl group.[100]



Scheme 2.39 *Regioselectivity Issues in Allylic Substituted-Cycloalkene Oxidation.*

2.2. Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of Cyclopentenes

2.2.1. Preliminary Results and Optimisation of Reaction Conditions

We envisaged that the cyclopentene **175** would provide a high degree of control in the regioselective hydrogen abstraction to afford the enones **177/178** (Fig. 2.11). The cyclopentene **175** would undergo a hydrogen abstraction to afford the allyl radical **176**, followed by the free-radical recombination, which depending on the steric bias of the quaternary centre will furnish either the enone **177** or **178** regioselectively.

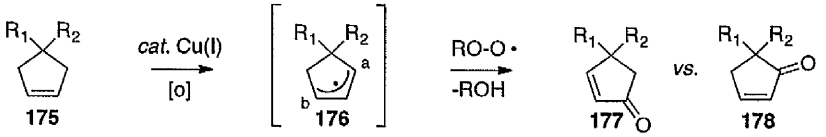
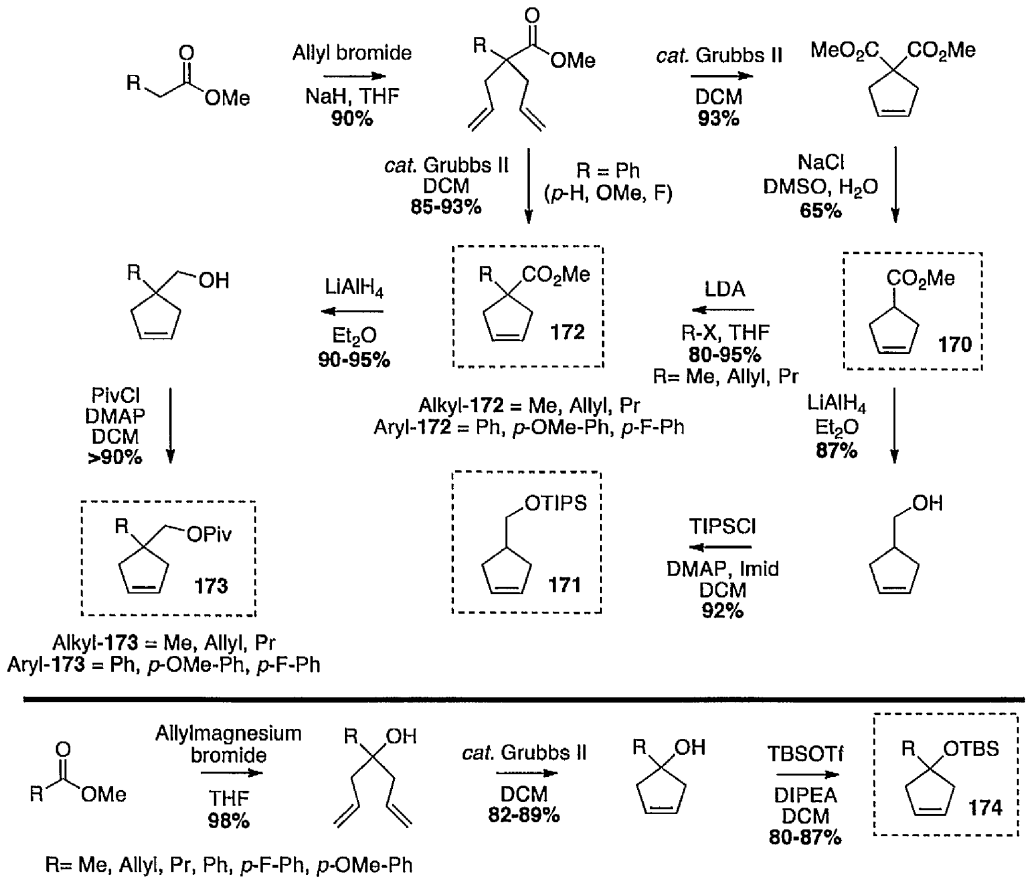


Figure 2.11 *Copper(I)-Catalysed Allylic Oxidation of Cyclopentene 175.*

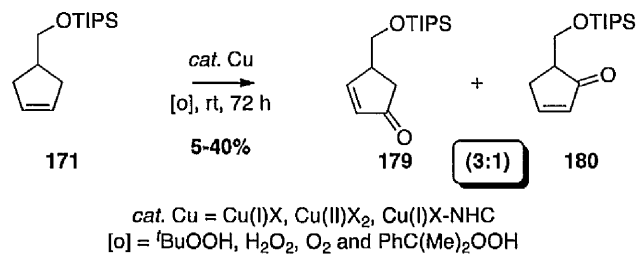
Preliminary studies examined the copper(I)-NHC catalysts, which were used for the formation of the allylic esters from cycloalkenes.[102] Substituted-cyclopentenes were prepared to test the efficiency and selectivity of the copper(I)-NHC-catalysed allylic oxidation reaction. Tertiary- and quaternary-substituted cyclopentenes **170-174** were prepared from readily available starting materials

(Scheme 2.40).[103] The methyl cyclopent-3-enecarboxylate **170** was utilised to synthesise the tertiary- and quaternary-substituted cyclopentenes as outlined in Scheme 2.40.[104]



Scheme 2.40 *Synthesis of Tertiary- and Quaternary-Substituted Cyclopentenes.*

Treatment of the tertiary-substituted cyclopentene **171** with a range of copper(I) and copper(II) salts (with and without NHC ligands) using different oxidants furnished the mixture of enones **179/180** in 40% yield and with poor regioselectivity, favouring of **179** (Scheme 2.41).



Scheme 2.41 *Copper-Catalysed Allylic Oxidation of Cyclopentene 171.*

The cyclopentene **171** presumably undergoes axial abstraction of either prochiral hydrogens to generate the allyl radical **171i** (Fig. 2.12). The major enone **179** would arise from the termination of the ^{t}BuOO• and the allyl radical **171i**, followed by the decomposition of the subsequent mixed peroxide (Path **A**). Additionally, the minor enone **180** would arise from the termination of the ^{t}BuOO• and the allyl radical **171i** (Path **B**). The formation of enone **180** could be prevented with elaborate functionalisation of the tertiary R group, preventing this recombination. However, it was envisaged that quaternary-substituted cyclopentenes would provide a more sterically demanding environment for the allylic oxidation thus avoiding the minor pathway observed in the tertiary-substituted cyclopentenes (Path **B**).

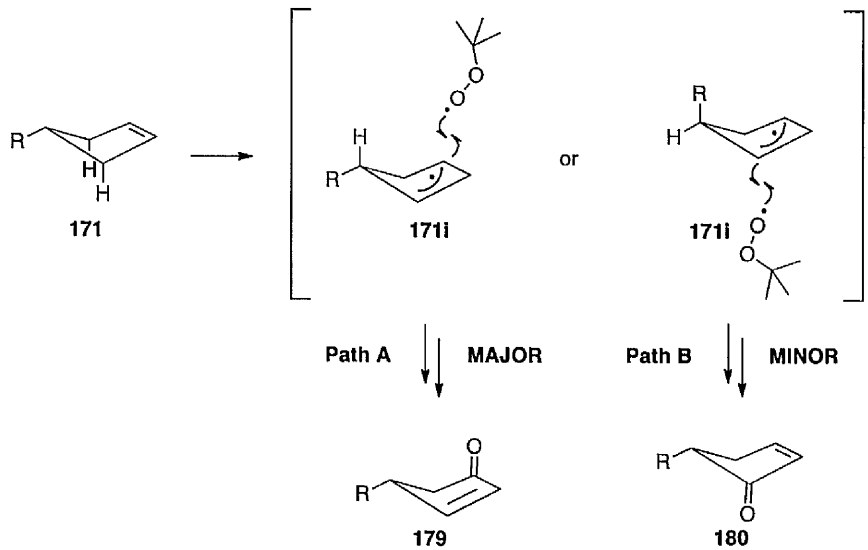
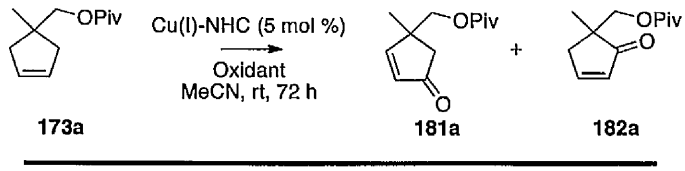


Figure 2.12 *Proposed Regioselectivity Pathways of Tertiary-Substituted Cyclopentene 171.*

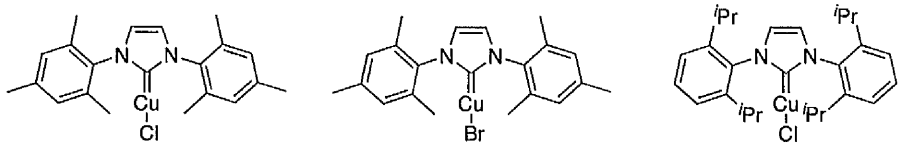
This reasoning was tested on the quaternary-substituted cyclopentene **173a** using different copper(I)-NHC catalysts and oxidants in acetonitrile at room temperature (Table 2.4). Gratifyingly, improved regioselectivity was observed for the oxidation of (1-methylcyclopent-3-en-1-yl)methyl pivalate **173a** to the enones **181a** and **182a** under the copper(I)-catalysed conditions (Table 2.4). Treatment of **173a**

with copper(I) chloride and *tert*-butyl hydroperoxide afforded a mixture of enones **181a/182a** (12:1) in 12% yield (Table 2.4, entry 1). This was further improved using the more sterically hindered chloride catalyst **183** in 29% yield, whereas the bromide **184** afforded a reduction in regioselectivity (entries 2 and 3). The more sterically hindered complex **185** provided similar reactivity to the chloride **183**, whilst investigations into other oxidants were unsuccessful (entries 4-6).

Table 2.4 *Preliminary Copper(I)-NHC-Catalysed Allylic Oxidation of Quaternary-Substituted Cyclopentene* ***173a.***[a]



173a **181a** **182a**



183 **184** **185**

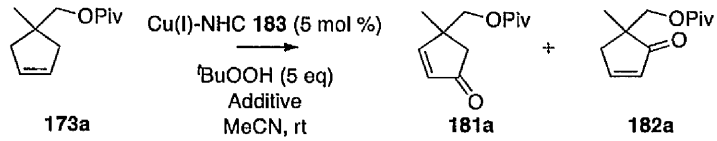
Entry	Catalyst (5 mol %)	Oxidant (5 eq)	181a:182a[b]	Yield[c] (%)
1	CuCl	^{t}BuOOH	12:1	12
2	***183***	***^{t}BuOOH***	***12:1***	***29***
3	**184**	^{t}BuOOH	8:1	28
4	**185**	^{t}BuOOH	12:1	27
5[d]	**183**	O_2	-	0
6	**183**	$PhC(Me)_2OOH$	12:1	17

[a]Reactions were performed on 0.25 mmol scale. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields. [d]1 atm of O_2.

It was envisioned that additives would improve the efficiency of the reaction through their ability to promote elimination of the peroxyether intermediate.[77,89,97] Table 2.5 outlines this investigation, in which the addition of 3Å MS and bases was examined. For example, the addition of 3Å MS did not improve the efficiency, providing similar mixtures of the enones (Table 2.5, entry 1). Sodium acetate was

detrimental in the oxidation reaction and resulted in the reduction of regioselectivity in poor yield (entry 2). Carbonate bases were more effective with enhanced efficiency and lower reaction times (entries 3 and 4). Although the yield was improved, we believed that the poor conversion was due to the premature decomposition of the *tert*-butyl hydroperoxide under the reaction conditions, which prompted examination of the rate of addition of the oxidant.[105]

Table 2.5 *Additive Screen in Copper(I)-NHC-Catalysed Allylic Oxidation of Quaternary-Substituted Cyclopentene* ***173a.***[a]



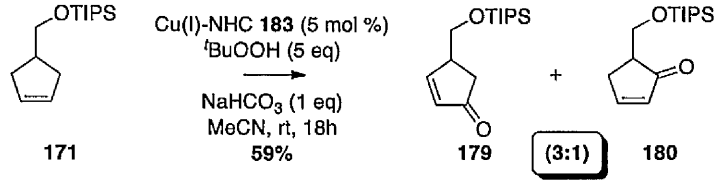
173a 181a 182a

Entry	Additive (1 eq)	Time (h)	181a:182a[b]	Yield[c] (%)
1[d]	3Å MS	72	12:1	27
2	NaOAc	72	7:1	30
3	K_2CO_3	48	12:1	47
4	$NaHCO_3$	24	12:1	49
5[e]	$NaHCO_3$	24	18:1	65
6[e,f]	***$NaHCO_3$***	***18***	***18:1***	***79***

[a]Reactions were performed on 0.25 mmol scale. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields. [d]200 mg/mmol. [e]Syringe pump addition at 0.3 eq/h. [f]Reaction performed at 0.5 M concentration.

Gratifyingly, treatment of **173a** with the syringe-pump addition of the *tert*-butyl hydroperoxide over 12 hours, afforded **181a/182a** in 65% yield, favouring **181a** with 18:1 regioselectivity (Table 2.5, entry 5). An additional improvement in the oxidation reaction was obtained at higher concentration (0.1 M *vs.* 0.5 M) and in this case, enones **181a/182a** were furnished in 79% yield with excellent regioselectivity (entry 6). Interestingly, resubjection of the tertiary-substituted

cyclopentene **171** to the optimal conditions furnished a mixture of **179/180** in 59% yield with similar regioselectivity (Scheme 2.42).

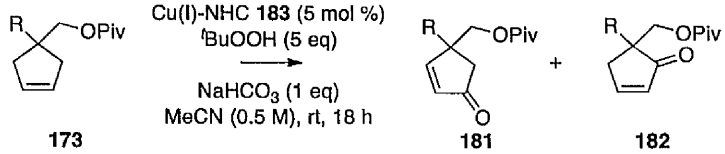


Scheme 2.42 *Resubmission of the Optimal Conditions to Tertiary-Substituted Cyclopentene 171.*

2.2.2. Scope and Limitations

With the optimal conditions in hand, the scope of the copper(I)-NHC-catalysed allylic oxidation was investigated. Table 2.6 outlines the resulting allylic oxidation of the CH_2-OPiv-substituted quaternary cyclopentenes **173** to the corresponding enones **181/182**. The oxidations all proceeded at room temperature with the syringe pump addition of *tert*-butyl hydroperoxide over 18 hours, utilising 5 mol % of copper(I)-NHC catalyst **183**.

Table 2.6 *Scope of CH_2-OPiv-Substituted Quaternary Cyclopentenes 173.*[a]



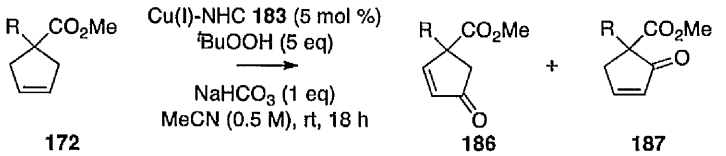
Entry	R		181:182[b]	Yield[c] (%)
1	Me	**173a**	18:1	80
2	Allyl	**173b**	≥19:1	77
3	*n*-Propyl	**173c**	≥19:1	81
4	*p*-OMe-Ph	**173d**	≥19:1	85
5	Ph	**173e**	≥19:1	84
6	*p*-F-Ph	**173f**	≥19:1	85

[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of tBuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields.

Alkyl substituents with increased steric bulk provided improved regioselectivity as expected (Table 2.6, entries 1-3). Substrates bearing aryl substituents underwent reaction with exceptional yields and regioselectivities; both the electron-deficient and electron-rich examples were suitable substrates (entries 4-6). Interestingly, reaction of the allyl substituted cyclopentene **173b** afforded the enone **181b** without competitive oxidation of the acyclic alkene (entry 2). This was attributed to the 4 kcal/mol difference in BDE between the cyclic and acyclic allylic hydrogens (cyclic ≈ 82 kcal/mol, acyclic ≈ 86 kcal/mol).[9]

Additional studies focused on other substituted cyclopentenes. Table 2.7 outlines the allylic oxidation reaction of the ester-substituted quaternary cyclopentenes **172** to the corresponding enones **186/187**.

Table 2.7 *Scope of CO_2Me-Substituted Quaternary Cyclopentenes 172.*[a]



172 186 187

Entry	R		186:187[b]	Yield[c] (%)
1	Me	**172a**	10:1	77
2	Allyl	**172b**	14:1	74
3	*n*-Propyl	**172c**	16:1	80
4	*p*-OMe-Ph	**172d**	≥19:1	82
5	Ph	**172e**	≥19:1	84
6	*p*-F-Ph	**172f**	≥19:1	84

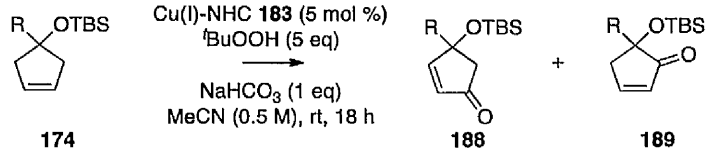
[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of ^{t}BuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields.

The copper(I)-NHC-catalysed allylic oxidation reactions of the electron-deficient ester-substituted cyclopentenes **172** proceeded with lower regioselectivities, albeit in excellent yields. This study illustrates the same trend in selectivity with substrates bearing bulkier alkyl groups undergoing more selective oxidation (Table

2.7, entries 1-3). Substrates bearing aryl substituents once again undergo completely regioselective oxidation (entries 4-6).

Table 2.8 outlines the resulting allylic oxidation of the *tert*-butyldimethylsilyl protected hydroxy-substituted quaternary cyclopentenes **174**. The copper(I)-NHC-catalysed allylic oxidation reaction furnished the enones **188/189** with excellent yields (Table 2.8, entries 1-6). Interestingly, the methyl-substituted derivative **174a**, which provided lower selectivity for **172a** and **173a**, underwent oxidation with excellent results in this case (entry 1).

Table 2.8 *Scope of OTBS-Substituted Quaternary Cyclopentenes 174.*[a]



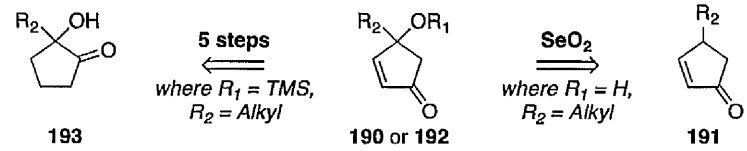
174 188 189

Entry	R		188:189[b]	Yield[c] (%)
1	Me	**174a**	≥19:1	72
2	Allyl	**174b**	≥19:1	70
3	*n*-Propyl	**174c**	≥19:1	75
4	*p*-OMe-Ph	**174d**	≥19:1	81
5	Ph	**174e**	≥19:1	81
6	*p*-F-Ph	**174f**	≥19:1	83

[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of ^{t}BuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields.

The hydroxyl-substituted enones provide valuable motifs for further derivatisation, which are not normally prepared *via* the metal-catalysed allylic oxidation (Scheme 2.43). For example, the tertiary alcohol **190**, where R_1 = H, can be prepared from the enone **191** using stoichiometric selenium dioxide.[107] Alternatively, the tertiary silyl ether **192**, where R_1 = TMS, is available from the tertiary alcohol **193** through a five-step sequence (Scheme 2.43).[108] These reactions validate the synthetic value of the copper(I)-NHC-catalysed allylic oxidation reaction of

homoallylic alcohols to the corresponding enones, which circumvents the necessity for toxic reagents and multi-step transformations.



Scheme 2.43 *Traditional Syntheses of Enone **190** or **192**.*

Based on the data, mechanistic pathways are proposed for the formation of the enones **195** and **196** from the cyclopentene **194** (Figure 2.13). Analogous to the proposed mechanism for the tertiary-substituted cyclopentenes, the cyclopentene **194** undergo allylic hydrogen abstraction to afford the allyl radical **194i** (Fig. 2.13). The termination of the ^{t}BuOO• **59** with **194i** would favour path **A** over path **B** due to steric encumbrance of the quaternary centre, leading to the highly regioselective formation of enone **195** over **196**.

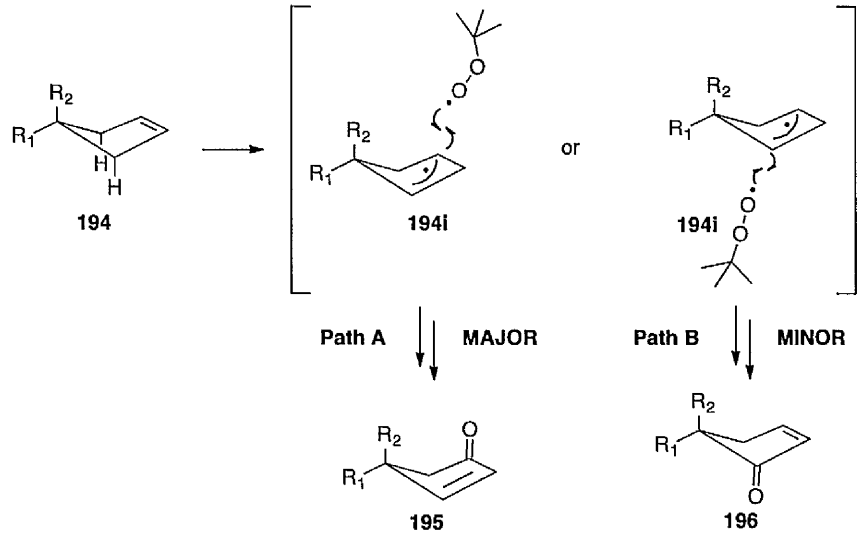
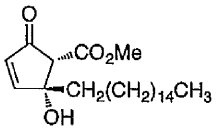


Figure 2.13 *Proposed Pathways for Regioselectivity of Quaternary-Substituted Cyclopentenes **194**.*

2.2.3. Total Synthesis of (±)-Untenone A

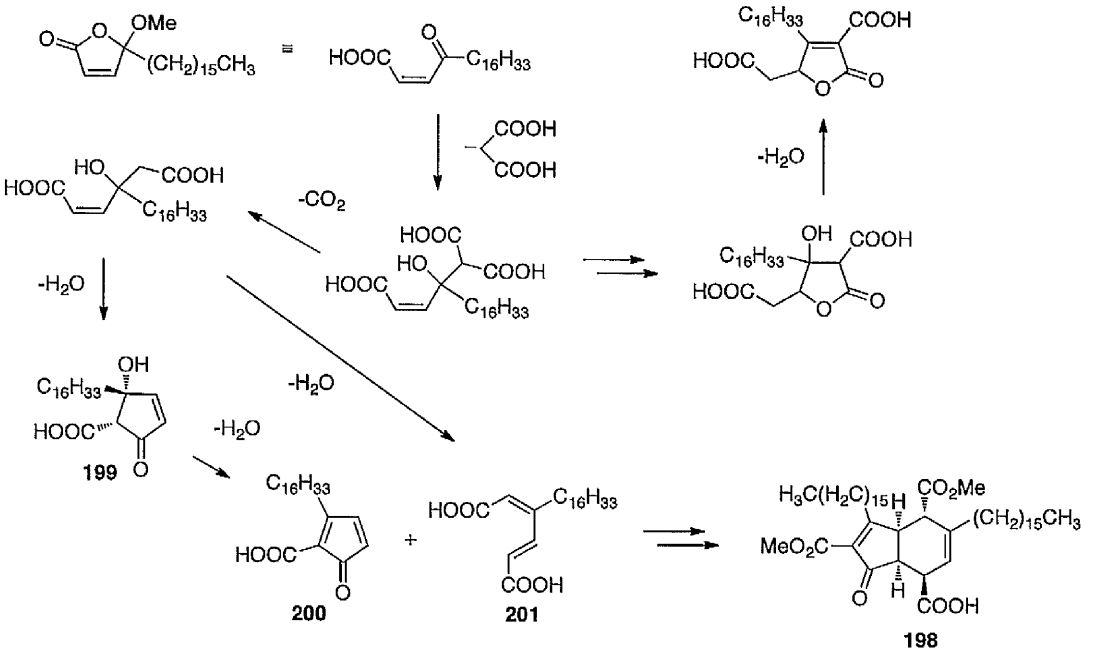
2.2.3.1. Background and Significance

Untenone A **197**, a marine natural product, derived from the biosynthetic pathway of manzamenones, was isolated from the Okinawan marine sponges of the genus *Plakortis* by Kobayashi *et al* in 1993. It provides a dienophile in the biosynthesis of manzamenones, more specifically, manzamenone A **198**.[109]



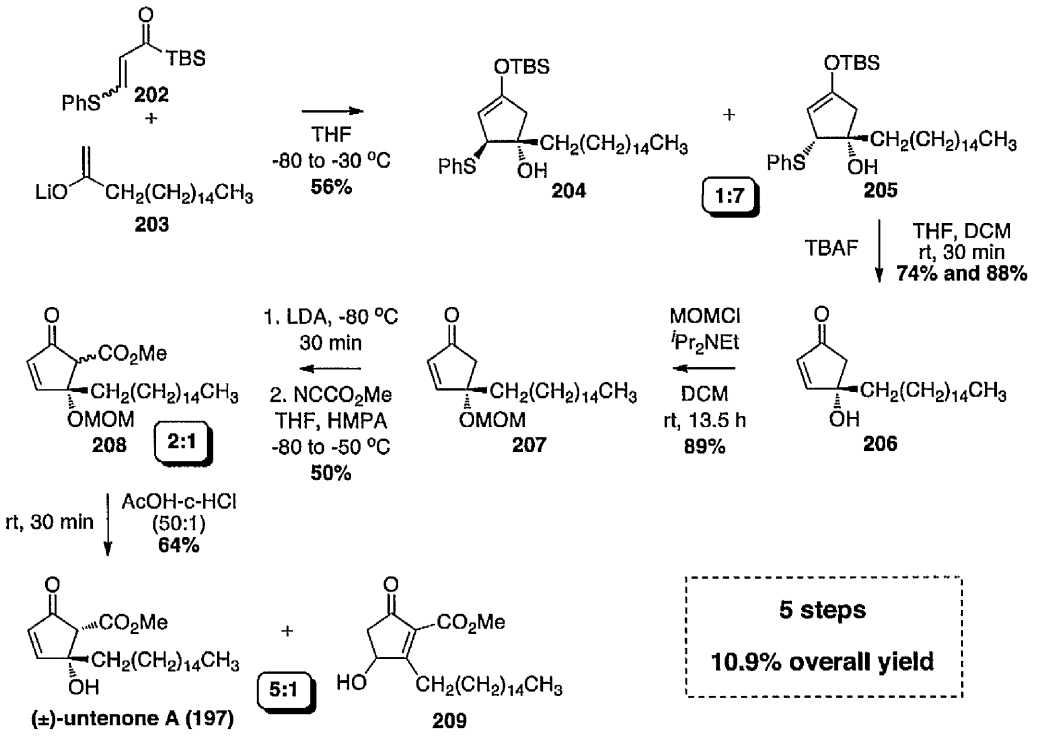
(±)-untenone A (197)

Untenone A **198** is reported to inhibit the cell proliferation of L1210 cells and the activity of DNA polymerases. Scheme 2.44 highlights the proposed biosynthetic pathway of manzamenones and the role of untenone A **197**. Manzamenone A **198** is thought to be derived from the intermolecular [4+2] cycloaddition between the dienophile **200** (dehydrated **199**) and the diene **201** (dehydrated precursor of **199**) (Scheme 2.44). The isolation of **199** therefore provides compelling evidence for this biosynthesis proposal.[109]



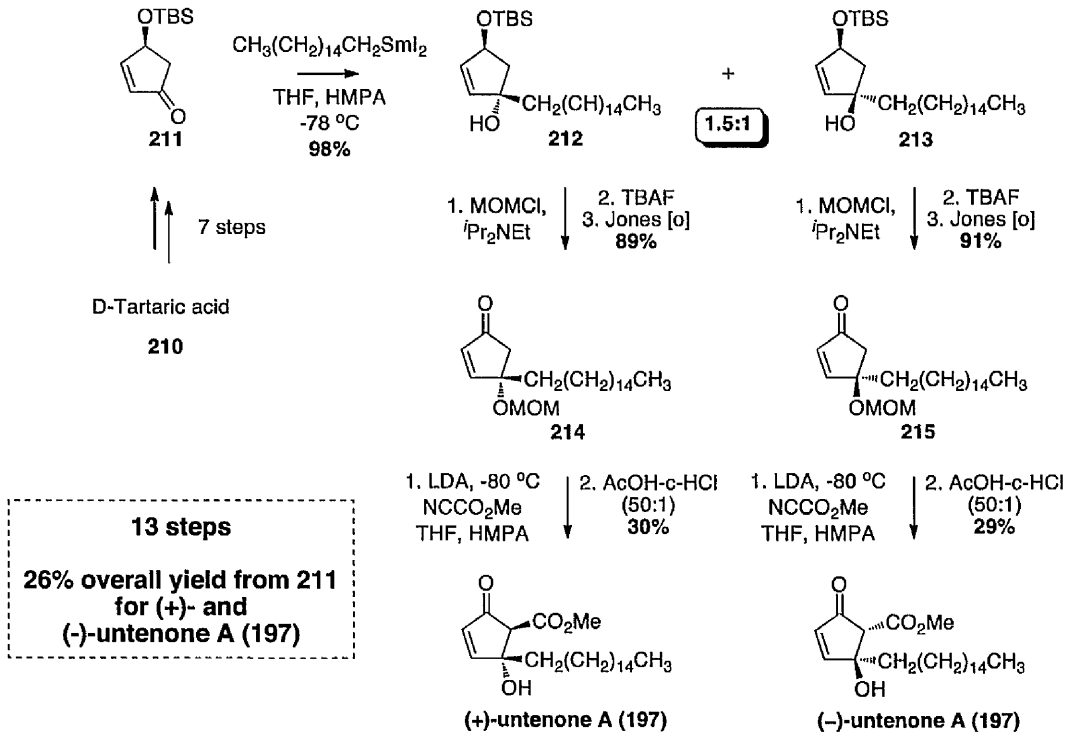
Scheme 2.44 *Proposed Biosynthesis of Manzamenone A* ***198****.*

There have been a plethora of racemic and asymmetric total syntheses of untenone A **197**. In 1994, Takeda *el al.* described the first racemic total synthesis of (±)-untenone A **197** in 5 steps (Scheme 2.45).[110]



Scheme 2.45 *First Reported Racemic Total Synthesis of (±)-Untenone A 197.*

Treatment of *β*-(phenylthio)acryloyl *tert*-butyldimethylsilane **202** with the lithium enolate **203** afforded the cyclopentenols **204/205** in 56% yield as 1:7 mixture of diastereomers (Scheme 2.45).[110] Cyclopentenols **204/205** were individually subjected to deprotection under TBAF conditions to furnish the cyclopentenol **206** in 88% yield. MOM protection of **206** provided the ether **207**, which was subjected to methoxycarbonylation with LDA and Mander's reagent provided a 2:1 epimeric mixture of the β-keto esters **208** in 50% yield. Treatment of the *β*-keto esters **208** with AcOH/HCl (50:1) afforded (±)-untenone A **197** in 54% yield along with its isomer **209** in 10% yield. The expedient 5-step synthesis provides (±)-untenone A **197** in 10.9% overall yield.[110]



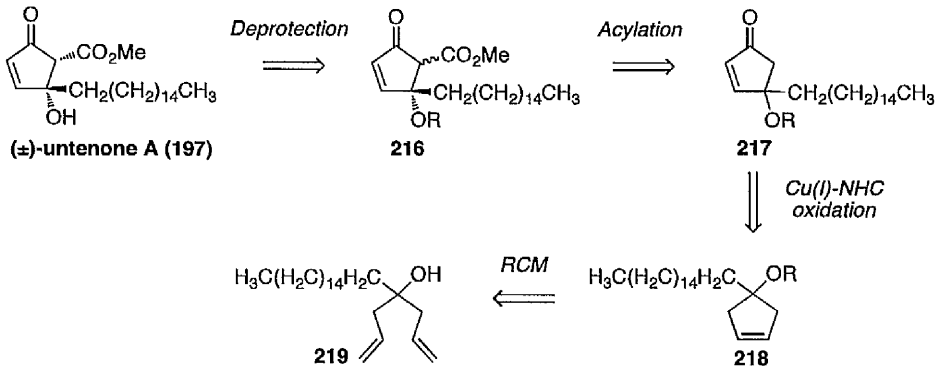
Scheme 2.46 *First Reported Asymmetric Total Syntheses of (+)- and (-)-Untenone A 197.*

In 1995, Yamada *et al.* described the first asymmetric total synthesis of (+)- and (−)-untenone A **197** in 13 steps from D-tartaric acid **210** (Scheme 2.46).[111] Treatment of the cyclopentenone **211** (prepared in 7 steps from D-tartaric acid **210**) with the alkylsamarium(III) reagent afforded a diastereomeric mixture of **212/213** in 98% yield (Scheme 2.46).[112] Methoxy methyl protection of the alcohol **212** and subsequent TBAF deprotection/Jones oxidation furnished the enone **214** in 89% yield.[111] Acylation of the enone **214** provided a mixture of *β*-keto esters in a 3:2 diastereomeric mixture. Acid-mediated MOM deprotection of **214** to provided (+)-untenone A **197** in 26% overall yield from **211**, and 13 steps from D-tartaric acid **210**. (−)-Untenone A **197** was prepared from the diastereomeric alcohol **213** in a comparable 26% overall yield from **211**, and 13 steps from D-tartaric acid **210**.[111,112]

The asymmetric syntheses of (+)- and (−)-untenone A **197** were important because the two enantiomers exhibit a Cotton effect, whilst natural untenone A **197** did not exert this effect, demonstrating that the natural product is actually racemic.[111]

2.2.3.2. Total Synthesis of (±)-Untenone A

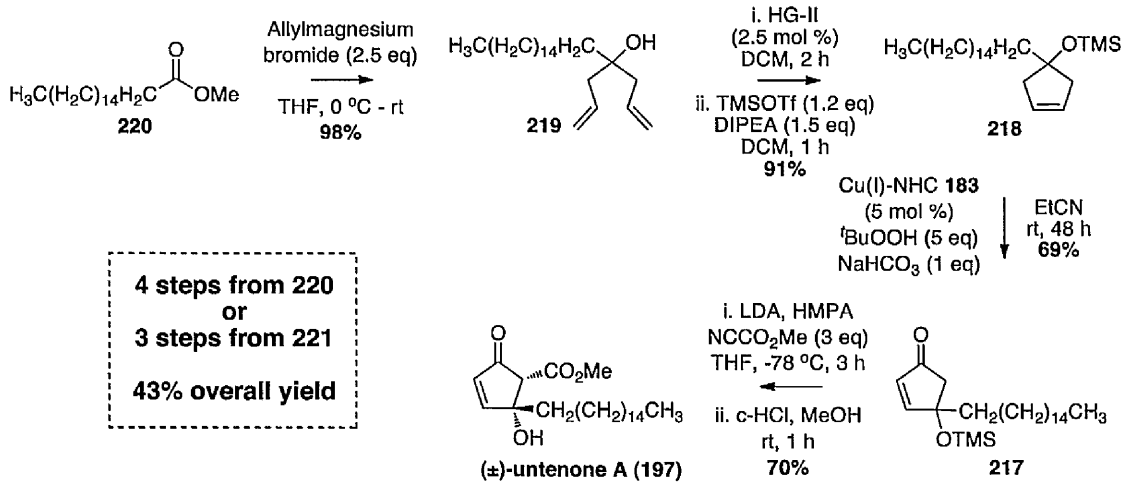
We envisaged that (±)-untenone A **197** would be derived from the acylation/deprotection of enone **217** (Scheme 2.47). Enone **217** is a common intermediate reported in previous total syntheses and a product that can be accessed from the regioselective copper(I)-NHC-catalysed allylic oxidation of the cyclopentene **218**.[110,111] The cyclopentene **218** is readily prepared *via* the ring-closing metathesis of the known *bis*-allyl tertiary alcohol **219**.[113]



Scheme 2.47 *Retroanalysis of (±)-Untenone A 197.*

The total synthesis of (±)-untenone A **197** commenced with the treatment of methyl heptadecanoate **220** with allylmagnesium bromide to afford the tertiary alcohol **219** in 98% yield (Scheme 2.48).[113] Hoveyda-Grubbs II ring-closing metathesis of alcohol **219** followed by the TMS protection provided the cyclopentene **218** in 91% yield. This set up the key copper(I)-NHC-catalysed allylic oxidation.[102] Gratifyingly, exposure of the cyclopentene **218** to the modified allylic oxidation conditions furnished the cyclopentenone **217** in 69% yield as a single regioisomer. Due to the lipophilic nature of the cyclopentene **218**, the solvent was changed to propionitrile for the dissolution of the substrate under the reaction conditions, which allowed for complete conversion after 48 hours. Treatment of the enolate generated from ketone **217** with Mander's reagent and concomitant acid deprotection afforded (±)-untenone A **197** in 70% yield.[114] This represents the most efficient (43% overall

yield) and highly expedient (4 steps from methyl heptadecanoate **220** or 3 steps from known alcohol **219**) total synthesis of (±)-untenone A **197** developed to date.



Scheme 2.48 *Highly Expedient and Efficient Total Synthesis of (±)-Untenone A* ***197****.*

2.3. Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of Cyclohexenes

2.3.1. Preliminary Results and Optimisation of Reaction Conditions

Having established that copper(I)-NHC catalysis provides highly regioselective and efficient allylic oxidations of prochiral quaternary-substituted cyclopentenes, we elected to examine related cycloalkene systems.[102]

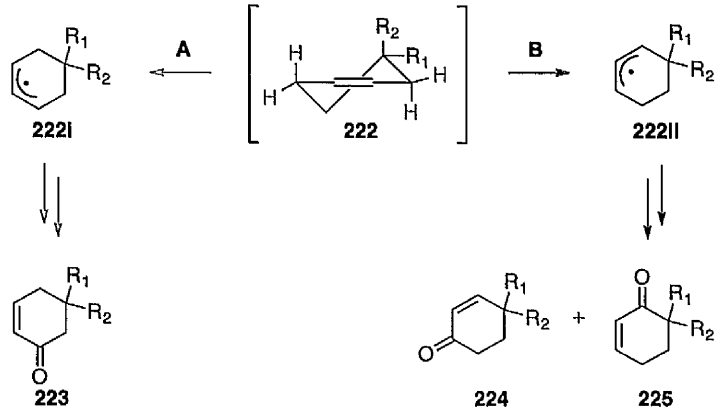
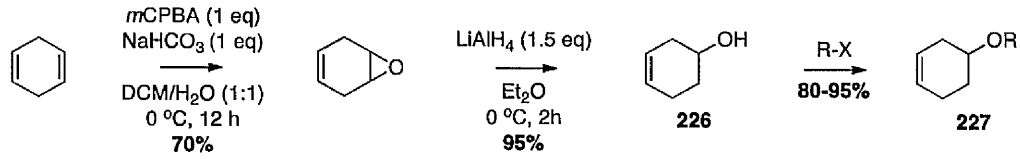


Figure 2.14 *Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of Ternary-Substituted Cyclohexene Concept.*

We envisioned that the ternary-substituted cyclohexene **222** would undergo a regioselective hydrogen abstraction to afford the allyl radical **222i** (Path **A**) rather

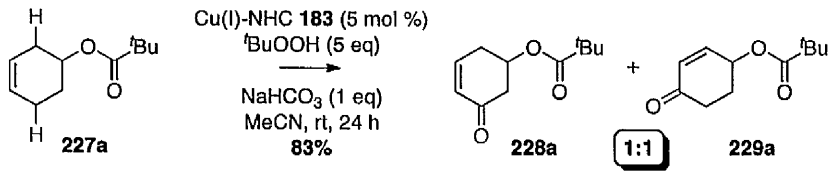
than **222ii** (Path **B**) depending on the steric environment (Fig. 2.14). Cyclohexene **222** could theoretically lead to three oxidation products, the enones **223**, **224** and **225**.

The preparation of the alkoxy substituted-cyclohexenes **227** was achieved *via* the epoxidation/ring-opening of commercially available 1,4-cyclohexadiene to furnish the cyclohexenol **226**, which can be further derivatised with an array of electrophiles (Scheme 2.49).[115]



Scheme 2.49 *Synthesis of Oxygen Ternary-Cyclohexenes 227.*

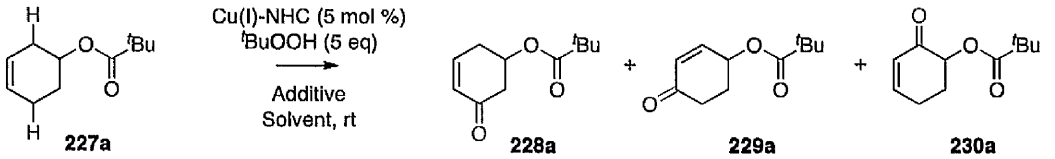
Treatment of the pivalate ester substituted-cyclohexene **227a** with the copper(I)-NHC conditions afforded a mixture of the enones **228a/229a** in 83% yield as a 1:1 mixture of constitutional isomers (Scheme 2.50).[92] This result indicates that hydrogens at both allylic sites are capable of equal abstraction to generate the allyl radicals **222i** and **222ii**, which undergoes free-radical termination (Fig. 2.11).

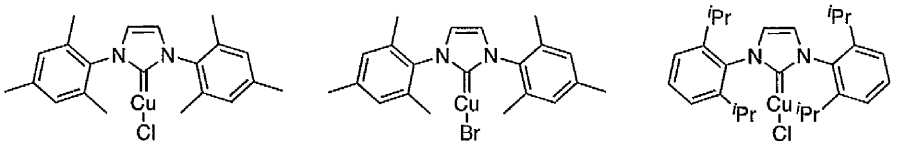


Scheme 2.50 *Initial Investigation into the Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of OPiv-Substituted Cyclohexene **227a**.*

The selectivity for the formation of **229a** is interesting, since there are two inequivalent positions in **222ii**, whereas **222i** provides a prochiral intermediate that leads to the same constitutional isomer. We envisaged that other groups might influence regioselective allylic hydrogen abstraction.

Table 2.9 *Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of OPiv-Substituted Cyclohexene* ***227a*** *Optimisation.*[a]





183 **184** **185**

Entry	Cu(I)-NHC	Additive (1 eq)	Solvent	Conv. (%)	228a:229a:230a[b]	Yield[c] (%)
1[d]	***183***	***$NaHCO_3$***	***MeCN***	***100***	***1:1:0***	***83***
2[e]	**183**	-	MeCN	79	1:1:0	55
3[e]	**183**	Na_2CO_3	MeCN	76	1:1:0	45
4[e]	**183**	K_2CO_3	MeCN	75	1:1:0	41
5[e]	***183***	*$NaHCO_3$*	*MeCN*	*74*	*1:1:0*	*59*
6[e]	**184**	$NaHCO_3$	MeCN	62	1:1:0	47
7[e]	**185**	$NaHCO_3$	MeCN	65	1:1:0	47
8[e]	**183**	$NaHCO_3$	DCM	52	1:1:0	26
9[e]	**183**	$NaHCO_3$	PhH	41	1:1:0	19
10[e,f]	**183**	$NaHCO_3$	MeCN	52	1:1:0	42

[a]Reactions were performed on 0.25 mmol scale under air for 48 hours. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields. [d]Syringe pump addition of oxidant at 0.3 eq/h and stirred for 24 hours. [e]Oxidant added in one portion. [f]Performed at 60 °C.

Table 2.09 outlines the optimisation of this transformation. Treatment of **227a** under the standard conditions afforded a 1:1:0 mixture of the enones **228a/229a/230a** in 83% yield using copper(I)-NHC catalyst **183**, sodium bicarbonate and syringe-pump addition of *tert*-butyl hydroperoxide (Table 2.09, entry 1). The addition of the hydroperoxide in one portion in the absence of base provided the same selectivity, albeit with lower yield (entry 2). Other inorganic bases provided

lower yields with comparable levels of regioselectivity, as did various copper(I)-NHC catalysts, solvents and elevated reaction temperatures (entries 3-10).

2.3.2. Scope and Limitations

Additional studies focused on the examination of substituents to control regioselectivity using the optimised conditions summarised in Table 2.10. Interestingly, the phenyl carbonate **227b** and carbamate **227c** provided a 2:1 mixture of **228b/229b** and **228c/229c**, whereas the tosyl carbamate **227d** furnished a 10:1 mixture of **228d/229d** (entries 2-4). This result was intriguing since the former have sp^2 attachment, whereas the latter is sp^3. Hence, the SO_2 linker is more flexible and may lead to π-π-stacking with the alkene to shield the hydrogen from subsequent abstraction (Fig 2.15).

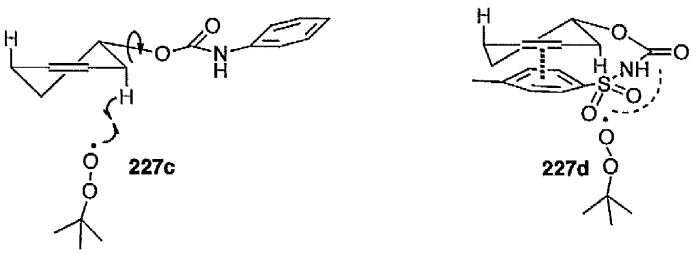
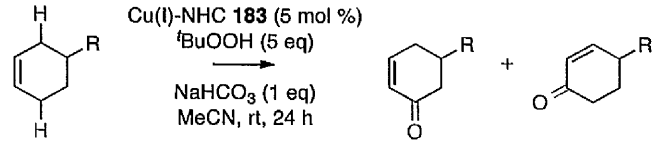


Figure 2.15 *Proposed π-Stacking Model for Phenyl Carbamate 227c vs. Tosyl Carbamate 227d.*

Additionally, the TBS ether **227e** and TBDPS ether **227f** provided a 6:1 and 11:1 mixture of **228e/229e** and **228f/229f**, respectively (Table 2.10, entries 5-6). This observation is somewhat surprising as silyl ethers generally have decreasing A-values as the silyl group increases in size (OTMS = 1.31, OTBS = 1.06, OTBDPS = 0.56 kcal/mol) compared to the alkyl ethers (OMe = 0.75, OEt = 0.90 kcal/mol), owing to the longer O-Si bond.[120] Hence, although the A-value predicts the TBS ether should provide enhanced selectivity compared to the TBDPS ether, this is not the case. Gratifyingly, the methyoxy ethyl ether **227h** afforded a ≥19:1 mixture of

228h/229h in 75% yield. Interestingly, the methoxy methyl ether **227g**, which should be similar in size to the methoxy ethyl ether **227h** provided a 6:1 mixture of **228g/229g**, which suggests that this is the result of a conformational bias rather than a steric preference (entry 7 *vs.* entry 8).

Table 2.10 *Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of O-Substituted Cyclohexenes 227 Scope.*[a]



227 228 229

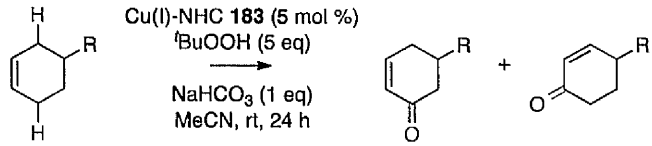
Entry	R		228:229[b]	Yield[c] (%)
1	OCO^tBu	**227a**	1:1	83
2	OCO_2Ph	**227b**	2:1	83
3	OCONHPh	**227c**	2:1	82
4	*OCONHTs*	*227d*	*10:1*	*81*
5	OTBS	**227e**	6:1	75
6	*OTBDPS*	*227f*	*11:1*	*74*
7	OCH_2OMe	**227g**	6:1	73
8[d]	*$O(CH_2)_2OMe$*	*227h*	*≥19:1*	*75*

[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of ^{t}BuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields. [d]After 48 hours.

Table 2.11 outlines the study of the oxidation of C-substituted cyclohexenes under the optimal conditions. Primary alcohols with varying protecting groups: electron deficient (pivalate ester **231a**) and electron rich (*tert*-butyldiphenyl silyl ether **231b**) all provided similar selectivity for the enones **232a/233a** and **232b/233b** (Table 2.11, entries 1-2). From these observations, it was postulated that electronic factors did not govern the regioselectivity, either in the allylic hydrogen abstraction or the termination processes. The size of the substituent does not seem to influence

the regioselectivity, since substitutions with a methylene linker have comparable A-values [CH_2CH_3 = 1.75, $CH_2C(CH_3)_3$ = 2.0 kcal/mol].[121]

Table 2.11 *Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of C-Substituted Cyclohexenes **231** Scope.*[a]



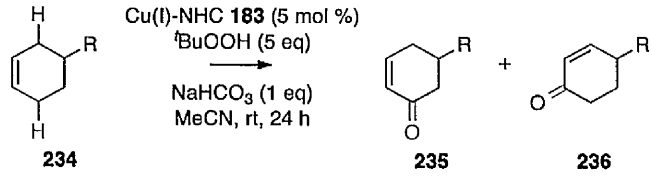
231 232 233

Entry	R		232:233[b]	Yield[c] (%)
1	CH_2OCO^tBu	**231a**	3:1	78
2	$CH_2OTBDPS$	**231b**	3:1	83
3	$CH(CH_3)OTBS$	**231c**	7:1	74
4	$CH(CH_3)OTBDPS$	**231d**	9:1	81
5	*$C(CH_3)_2OTBS$*	***231e***	*12:1*	*83*

[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of ^{t}BuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields.

Reaction of the secondary TBS ether **231c** under the optimal conditions afforded a 7:1 mixture of **232c/233c** in 74% yield, which is further improved when the TBDPS ether **231d** is used as a substrate (Table 2.11, entries 3 and 4). Interestingly, the secondary substituent provided a significant improvement (entries 3 *vs.* 5), which was predicted as the A-values rise for increasing carbon substitution (Et = 1.75, ^{i}Pr = 2.15, ^{t}Bu = >4.5 kcal/mol).[121] With this trend in mind, it was logical to prepare the ternary TBS ether **231e**. Gratifyingly, the ternary TBS ether **231e** furnished a 12:1 mixture of **232e/233e** in 83% yield, indicating that for carbon substituents the steric parameter is critical (entry 5).

Table 2.12 *Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of N-Substituted Cyclohexenes 234 Scope.*[a]



Entry	R		235:236[b]	Yield[c] (%)
1	NPhth	**234a**	10:1	83
2[d]	NHTs	**234b**	10:1	83
3[d]	NHBoc	**234c**	14:1	72
4[d]	NHTFA	**234d**	14:1	74
5[d]	$N(CH_3)Boc$	**234e**	16:1	69
6	*NBocOBoc*	*234f*	*≥19:1*	*75*

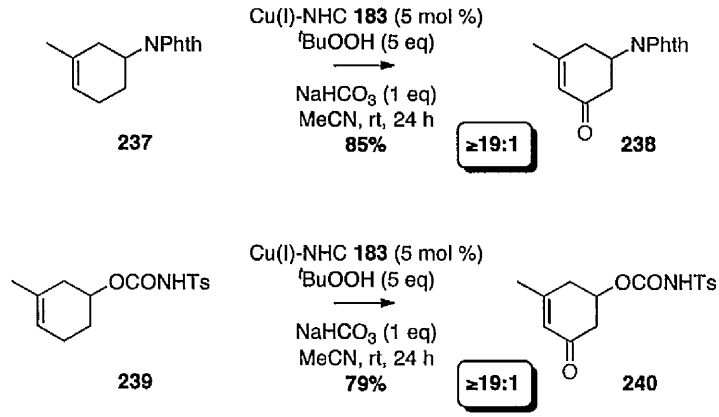
[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of [t]BuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields. [d]After 48 hours.

N-substituted cyclohexenes provided excellent regioselectivities in all cases with a plethora of protecting groups, with both secondary and tertiary nitrogen examples demonstrating exceptional reactivity (Table 2.12). Treatment of the phthalimide substituted cyclohexene **234a** under the optimal conditions furnished a 10:1 mixture of **235a/236a** in 83% yield after 24 hours (Table 2.12, entry 1). The allylic oxidation of compounds containing a nitrogen substituent can be troublesome because of chelation to metal catalysts.[122,123] Interestingly, the sulfinamide **234b**, carbamate **234c** and amide **234d** reacted in good yield and with excellent selectivity (entries 2-4). The incorporation of the labile Boc and TFA protecting groups allows for the facile removal using acid (trifluoroacetic acid for the Boc group) or base (potassium carbonate/methanol for the TFA group) to access the free amine.[124] The tertiary carbamate **234e** provided a 16:1 mixture of **235e/236e** in 69% yield, compared to the analogous secondary Boc carbamate **234c** which afforded a 14:1 mixture, demonstrating that the additional substitution enhances the regioselectivity

(entry 5 *vs.* entry 3). This is shown to great effect with the employment of the sterically demanding *N*-Boc hydroxylamine **234f**, which furnished a ≥19:1 mixture of **235f/236f** in 75% yield.

The concept of copper(I)-NHC-catalysed allylic oxidation of ternary-substituted cyclohexenes provides good regioselectivity for the oxygen, carbon and nitrogen substitutions. The regiocontrol for the carbon and nitrogen substrates is related to the steric bulk of the substituent (estimated from A-values), whereas the oxygen substituent is related to the conformation.

It was proposed that the electronic aspects could override steric factors in the case of the oxygen substitution, with hyperconjugation potentially playing a key role in this transformation.[125] This is highlighted for the methoxy methyl ether **227g** and methoxy ethyl ether **227h**.[126] In these two systems, the two oxygen groups prefer to be in the Gauche conformer, owing to the dipole interactions of the oxygen lone pairs.[127] This Gauche interaction impedes bond rotation, effectively making the system more rigid.[128]



Scheme 2.51 *Highly Regioselective Copper(I)-NHC-Catalysed Allylic Oxidation of Tri-Substituted Alkenes 237 and 239.*

It has been reported that tri-substituted cycloalkenes provide exclusively one regioisomer in the metal-catalysed allylic oxidation using *tert*-butyl hydroperoxide, with the oxidation favouring the least hindered terminus of the alkene.[77,89,97] It was

envisaged that the combination of ring substituents and alkene substitution would provide enhanced regioselectivity.

Treatment of the phthalimide **237** and the tosyl sulfinamide **239** under the optimal conditions afforded the enones **238** and **240** in 85% and 79% yield, respectively with excellent selectivities of ≥19:1 (Scheme 2.51). Figure 2.16 highlights the proposed model for the increased regioselectivity with the tri-substituted alkene providing supplemental steric hindrance for the α-hydrogen to the R group.

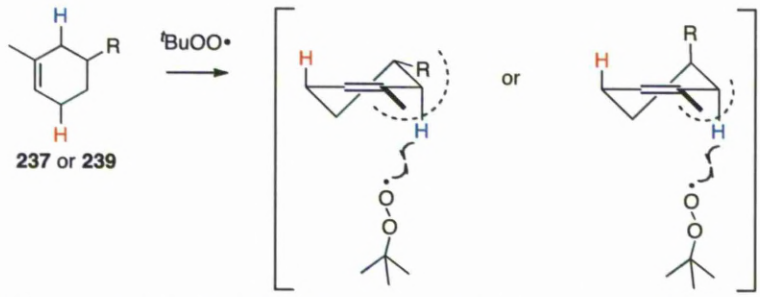
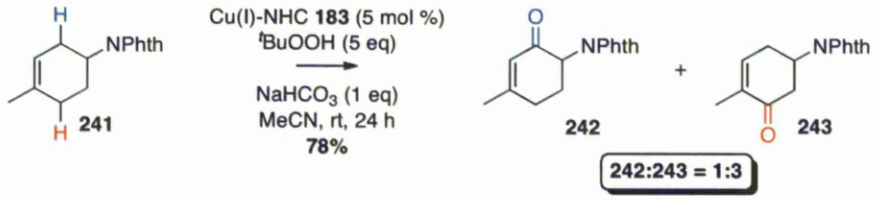


Figure 2.16 *Proposed Model for The Enhanced Regioselectivity of Tri-Substituted Alkenes 237 and 239.*

Interestingly, when the methyl group is placed on the other end of the alkene, e.g. phthalimide **241**, the major oxidation product is that where reaction has occurred at the hindered side of the alkene (Scheme 2.52). Phthalimide **241** provides competitive hydrogen abstraction, with the methyl and phthalimide groups offering differentiating steric hindrance to generate the enones **242** and **243**.



Scheme 2.52 *Substitution Competition Experiment of 241.*

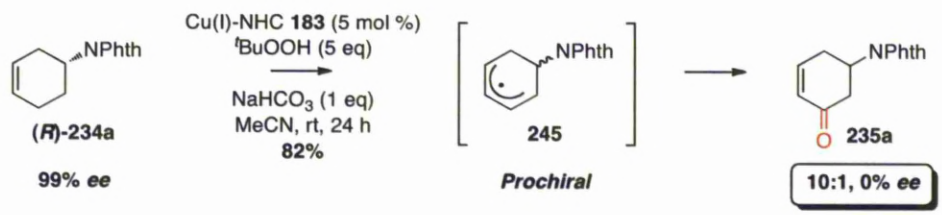
These motifs are synthetically useful building blocks, with the cyclohexenone **242**, essentially a α-substituted-amino enone, whereas cyclohexenone **243** would generally be prepared by a selenium dioxide oxidation.[54] We envisage that increased

regiocontrol can be achieved with careful manipulation of the substituents (type and position) to access either enones. Enantiopure phthalimide **(*R*)-237** was prepared by the Maruoka asymmetric allylation, 2nd Generation Hoveyda-Grubbs ring closing metathesis and Mitsunobu reaction sequence in 95% enantiomeric excess.[129] Treatment of the enantiopure phthalimide **(*R*)-237** under the optimal conditions furnished the enone **(*S*)-238** in 85% yield as a single regioisomer, and more importantly, with preservation of enantiopurity (Scheme 2.53).

Scheme 2.53 *Stereospecific Copper(I)-NHC-Catalysed Allylic Oxidation of Enantiopure Phthalimide* ***(R)-237****.*

2.3.3. Mechanistic Insights

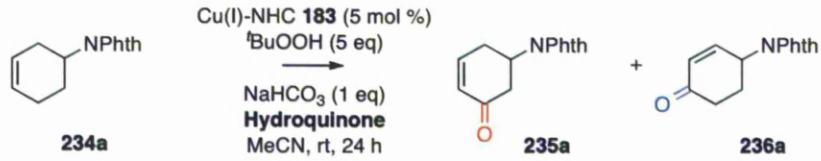
To investigate the reaction mechanism, the enantiopure phthalimide **(*R*)-234a** was prepared in 99% *ee* using similar sequence outlined for the tri-substituted phthalimide **(*R*)-237**, and subjected to the optimal oxidation conditions.[129] Treatment of the enantiopure phthalimide **(*R*)-234a** afforded a racemic mixture of enone **235a** in 82% yield (Scheme 2.54). Baldwin had previously suggested a prochiral allyl radical in the rhodium-catalysed autoxidation of (+)-carvomenthene **44**.[31] Hence, the symmetrisation of the phthalimide **(*R*)-234a** also provides the prochiral allyl radical **245**, which consequently affords the racemic enone **235a**.



Scheme 2.54 *Mechanistic Study to Probe the Prochiral Intermediate.*

A free radical pathway has been widely accepted for the mechanism of the metal-catalysed allylic oxidation reaction, and there have been many reports involving rhodium.[28,30,79] Generally, the use of a radical scavenger, e.g. hydroquinone, is utilised to inhibit the formation of free radicals. Table 2.13 outlines the investigation of the use of the free radical scavenger, hydroquinone in the copper(I)-NHC-catalysed allylic oxidation of the phthalimide **234a**. Treatment of **234a** under the optimal conditions with catalytic amount of hydroquinone and butylated hydroxytoluene (BHT) afforded the enone **235a** in 75% and 72% yield, respectively (entries 2 and 3). Although the copper(I)-NHC-catalysed allylic oxidation was suppressed when a stoichiometric amount of hydroquinone was added, this could result from the poisoning of the catalyst (entry 4).[79]

Table 2.13 *Free Radical Scavenger Effect.*[a]



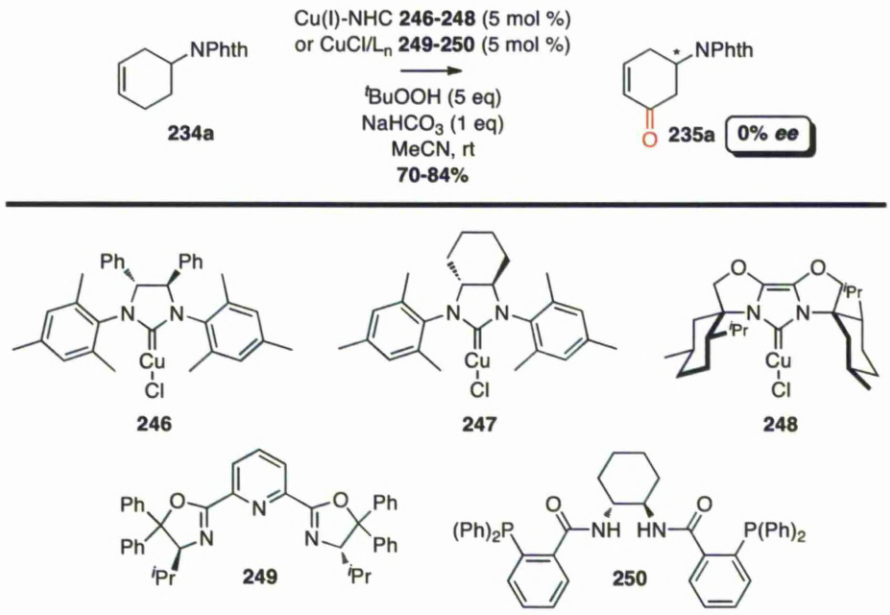
Entry	Hydroquinone (mol %)	235a:236a[b]	Yield[c] (%)
1	-	10:1	83
2	2	10:1	75
3[d]	2	10:1	72
4	100	-	-

[a]Reactions were performed on 0.25 mmol scale with syringe pump addition of ^{t}BuOOH at 0.3 eq/h. [b]Determined by ^{1}H-NMR on crude mixtures. [c]Isolated yields. [d]BHT was used.

2.3.4. Enantioselective Copper(I)-Catalysed Allylic Oxidation

The enantioselective copper-catalysed allylic oxidation reaction of the racemic phthalimide **234a** *via* the desymmetrisation of the prochiral allyl radical intermediate **245** to afford the enantiopure enone **235a** was investigated. Treatment

of racemic phthalimide **234a** with the copper(I)-NHC catalysts **246-248** and copper(I) chloride/ligand complexes **249-250** with *tert*-butyl hydroperoxide furnished the enone **235a** in up to 84% yield, but the product was racemic in all cases (Scheme 2.55).[130] These results were disappointing and demonstrates that the copper complex is not involved in the enantio-determining step of the oxidation reaction.



Scheme 2.55 *Efforts Towards the Enantioselective Copper-Catalysed Allylic Oxidation of Phthalimide* ***234a***.

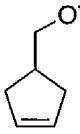
2.4 Conclusions

In conclusion, it has been demonstrated that copper(I)-NHC catalysts can be employed in the regioselective allylic oxidation of quaternary-substituted cyclopentenes and ternary-substituted cyclohexenes to give oxidised products in excellent yields and with good selectivities.[92,131] These processes require the slow addition of *tert*-butyl hydroperoxide to supress decomposition, allowing clean conversions and superior efficiencies. The quaternary-substituted cyclopentenes with an array of functional groups reacted in good regioselectivity.[92] The synthetic utility of this transformation was exhibited in the most efficient and expedient total

synthesis of (±)-untenone A reported to date.[92] The copper(I)-NHC-catalysed allylic oxidation of the ternary-substituted cyclohexenes provided an insight into the nature of the steric environment for optimal regiocontrol with oxygen, carbon and nitrogen substituents.[131] In the case of the cyclohexenes, steric influences were not necessarily the governing factor for high regioselectivity, with stereoelectronics playing an equally important role. Enhanced regioselectivities were observed for tri-substituted cyclohexenes, providing a stereospecific allylic oxidation route to synthetically useful enantiopure cyclohexenones.[131] The intermediacy of the prochiral allyl radical was confirmed, which was used unsuccessfully in an enantioselective version of the oxidation reaction.

2.5 Experimental

2.5.1. Experimental Procedures



(Cyclopent-3-en-1-ylmethoxy)triisopropylsilane 171.[143]

Colour and state: Colorless oil. R_f = 0.8 (Hexane 100%).

Representative Experimental Procedure: Methyl cyclopent-3-enecarboxylate **170** (0.63 g, 5 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.28 g, 7.5 mmol) in diethyl ether (50 mL) at 0 °C and stirred for 1 hour. The reaction was slowly quenched at 0 °C with saturated aqueous potassium sodium tartrate (50 mL) and extracted three times with diethyl ether (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude alcohol as a colourless oil. The crude alcohol was added to a mixture of DMAP (0.06 g, 0.5 mmol), imidazole (0.85 g, 12.5 mmol) in dichloromethane (50 mL) at 0 °C. To the reaction mixture was added chlorotriisopropylsilane (1.28 mL, 6 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with water (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane) furnished 1.18 g (93%) of **171**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65-5.61 (m, 2H), 3.56 (d, J = 6.8 Hz, 2H), 2.53-2.36 (m, 3H), 2.16-2.10 (m, 2H), 1.06-1.03 (m, 21H).

IR (Neat) 3055 (w), 2943 (m), 2866 (m), 1617 (w), 1461 (m), 1103 (vs) cm^{-1}.

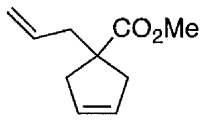
Methyl 1-methylcyclopent-3-enecarboxylate 172a.[132]

Colour and state: Pale yellow oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: To a solution of LDA, prepared from diisopropylamine (1.05 mL, 7.5 mmol) and *n*-butyllithium (2.5 M in hexanes, 3 mL, 7.5 mmol) in tetrahydrofuran (50 mL) at -78 °C was added dropwise methyl cyclopent-3-enecarboxylate **170** (0.63 g, 5 mmol). The reaction was maintained at -78 °C for 1 hour to which iodomethane (0.47 mL, 7.5 mmol) was added. The reaction mixture was slowly warmed to room temperature over 4 hours and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, 5-10% ethyl acetate/hexane) furnished the cyclopentene **172a** in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (bs, 2H), 3.69 (s, 3H), 2.92-2.89 (m, 2H), 2.24-2.21 (m, 2H), 1.30 (s, 3H).

IR (Neat) 2926 (w), 2853 (w), 1731 (vs), 1435 (w), 1274 (m), 1204 (s), 1119 (s) cm^{-1}.



Methyl 1-allylcyclopent-3-enecarboxylate 172b.

Colour and state: Pale yellow oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

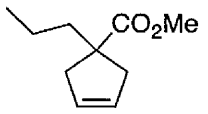
Representative Experimental Procedure: Prepared in accordance to **172a** using allylbromide (0.65 mL, 7.5 mmol) in 95%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74-5.66 (m, 1H), 5.66 (s, 2H), 5.05 (dd, J = 16.0 Hz, 1H), 5.05 (dd, J = 11.1 Hz, 1H), 3.69 (s, 3H), 2.85 (d, J = 14.3 Hz, 2H), 2.40 (d, J = 7.7 Hz, 2H), 2.34 (d, J = 14.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.71 (e), 134.40 (o), 128.47 (o), 117.99 (e), 52.05 (o), 51.96 (e), 43.48 (e), 42.10 (e).

IR (Neat) 3060 (w), 2925 (w), 2853 (w), 1731 (vs), 1640 (w), 1435 (m), 1260 (m), 1201 (s), 1135 (m), 916 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{10}H_{17}O_2$ 167.1023, found 169.1019.



Methyl 1-propylcyclopent-3-enecarboxylate 172c.

Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

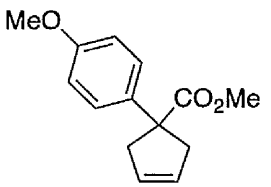
Representative Experimental Procedure: Prepared in accordance to **172a** using iodopropane (0.73 mL, 7.5 mmol) in 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (s, 2H), 3.71 (s, 3H), 2.91 (d, J = 14.5 Hz, 2H), 2.32 (d, J = 14.3 Hz, 2H), 1.69-1.65 (m, 2H), 1.29-1.21 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.32 (e), 128.62 (o), 52.72 (e), 51.97 (o), 42.47 (e), 42.10 (e), 18.78 (e), 14.61 (o).

IR (Neat) 3058 (w), 2957 (w), 2874 (w), 1732 (vs), 1622 (w), 1435 (m), 1298 (w), 1268 (w), 1205 (s), 1137 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{10}H_{17}O_2$ 169.1223, found 169.1219.



Methyl 1-(4-methoxyphenyl)cyclopent-3-enecarboxylate 172d.

Colour and state: Colorless solid. R_f = 0.5 (Hexane:Ethyl acetate = 90:10). mp = 31-33 °C.

Representative Experimental Procedure: To a solution of LDA, prepared from diisopropylamine (2.10 mL, 15 mmol) and *n*-butyllithium (2.5 M in hexanes, 6 mL, 15 mmol) in tetrahydrofuran (100 mL) at -78 °C was added dropwise methyl 2-(4-methoxyphenyl)acetate (1.80 g, 10 mmol). The reaction was maintained at -78 °C for

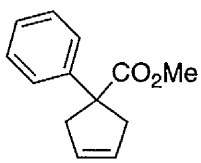
1 hour to which allyl bromide (1.30 mL, 15 mmol) was added. The reaction mixture was slowly warmed to room temperature over 4 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL), extracted three times with diethyl ether (100 mL) and washed with brine (200 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the monoalkylated ester. The above alkylation step was repeated to afford the dialkylated ester, where it added to a solution of 2nd Generation Grubb's catalyst (0.21 g, 2.5 mol %) in dichloromethane (100 mL). The reaction mixture was stirred for 2 hours, followed by the addition of dimethylsulfoxide (1.78 mL, 25 mmol), and then stirred for 12 hours. The mixture was concentrated *in vacuo* and purification by flash chromatography (silica, 5-10% ethyl acetate/hexane) furnished the cyclopentene **172d** in 86%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.75 (s, 2H), 3.79 (s, 3H), 3.63 (s, 3H), 3.39 (d, J = 14.5 Hz, 2H), 2.72 (d, J = 14.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.88 (e), 158.41 (e), 135.85 (e), 129.29 (o), 127.77 (o), 113.80 (o), 57.79 (e), 55.30 (o), 52.56 (o), 42.90 (e).

IR (Neat) 2952 (w), 2838 (w), 1728 (vs), 1611 (m), 1512 (vs), 1442 (m), 1295 (m), 1249 (s), 1224 (s), 1183 (s), 1164 (s), 1037 (m), 831 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{17}O_3$ 233.1172, found 233.1172.



Methyl 1-phenylcyclopent-3-enecarboxylate 172e.[133]

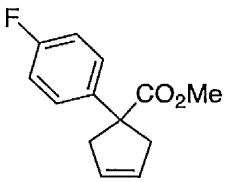
Colour and state: Colorless solid. R_f = 0.5 (Hexane:Ethyl acetate = 90:10). mp = 28-30 °C.

Representative Experimental Procedure: Prepared in accordance to **172d** using methyl 2-phenylacetate (1.50 g, 10 mmol) in 87%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.31 (m, 4H), 7.25-7.22 (m, 1H), 5.77 (s, 2H),

3.64 (s, 3H), 3.43-3.40 (m, 2H), 2.78-2.75 (m, 2H).

IR (Neat) 3059 (w), 2951 (w), 1729 (vs), 1495 (w), 1447 (w), 1260 (m), 1222 (s), 1164 (s) cm^{-1}.



Methyl 1-(4-fluorophenyl)cyclopent-3-enecarboxylate 172f.

Colour and state: Colorless oil. R_f = 0.3 (Hexane:Ethyl acetate = 95:5).

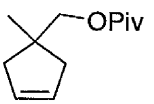
Representative Experimental Procedure: Prepared in accordance to **172d** using methyl 2-(4-fluorophenyl)acetate (1.68 g, 10 mmol) in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.99 (t, J = 8.8 Hz, 2H), 5.76 (s, 2H), 3.64 (s, 3H), 3.40 (d, J = 14.5 Hz, 2H), 2.72 (d, J = 14.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.41 (e), 161.68 (e, d, $J_{C\text{-}F}$ = 245.6Hz, CF), 139.42 (e, d, $J_{C\text{-}F}$ = 3.3 Hz, CCCCF), 129.16 (o), 128.26 (o, d, $J_{C\text{-}F}$ = 8.2 Hz, CCCF), 115.18 (o, d, $J_{C\text{-}F}$ = 21.3 Hz, CCF), 57.85 (e), 52.59 (o), 42.89 (e).

IR (Neat) 3060 (w), 2953 (w), 1730 (vs), 1606 (w), 1509 (vs), 1435 (m), 1261 (m), 1224 (s), 1193 (m), 1159 (s), 1056 (m), 835 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{13}H_{14}O_2F$ 221.0972, found 221.0973.



(1-Methylcyclopent-3-enyl)methyl pivalate 173a.

Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: Methyl 1-methylcyclopent-3-enecarboxylate **172a** (1.40 g, 10 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.57 g, 15 mmol) in diethyl ether (100 mL) at 0 °C and stirred for 1 hour. The reaction was slowly quenched at 0 °C with saturated aqueous potassium sodium tartrate (100 mL) and extracted three times with diethyl ether (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a

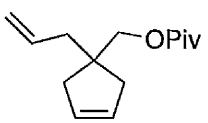
crude alcohol as a colourless oil. The crude alcohol was added to a mixture of DMAP (0.12 g, 1 mmol), triethylamine (2.09 mL, 15 mmol) in dichloromethane (50 mL) at 0 °C. To the reaction mixture was added trimethylacetyl chloride (1.85 mL, 15 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with saturated aqueous ammonium chloride (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, 5-10% ethyl acetate/hexane) furnished cyclopentene **173a** in 93%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (s, 2H), 3.90 (s, 2H), 2.31 (d, J = 13.9 Hz, 2H), 2.08 (d, J = 14.6 Hz, 2H), 1.23 (s, 3H), 1.20 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.81 (e), 129.00 (o), 71.81 (e), 43.43 (e), 41.66 (e), 39.06 (e), 27.33 (o), 25.37 (o).

IR (Neat) 3057 (w), 2962 (w), 2848 (w), 1730 (vs), 1702 (m), 1481 (m), 1283 (s), 1149 (vs) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{12}H_{21}O_2$ 197.1536, found 197.1530.



(1-Allylcyclopent-3-enyl)methyl pivalate 173b.

Colour and state: Pale yellow oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

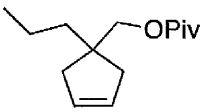
Representative Experimental Procedure: Prepared in accordance to **173a** using methyl 1-allylcyclopent-3-enecarboxylate **172b** (1.66 g, 10 mmol) in 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77-5.72 (m, 1H), 5.59 (s, 2H), 5.07-5.04 (m, 2H), 3.91 (s, 2H), 2.25-2.22 (m, 6H), 1.21 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.63 (e), 134.87 (o), 128.96 (o), 117.69 (e), 69.76 (e), 44.59 (e), 42.21 (e), 41.28 (e), 39.03 (e), 27.32 (o).

IR (Neat) 3078 (w), 2976 (w), 2906 (w), 2848 (w), 1730 (vs), 1640 (w), 1480 (m), 1282 (s), 1157 (vs), 1034 (w), 992 (w), 914 (s), 734 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{23}O_2$ 223.1693, found 223.1691.



(1-Propylcyclopent-3-enyl)methyl pivalate 173c.

Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

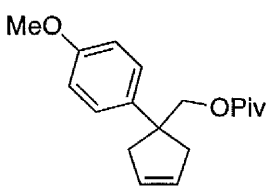
Representative Experimental Procedure: Prepared in accordance to **173a** using methyl 1-propylcyclopent-3-enecarboxylate **172c** (1.68 g, 10 mmol) in 91%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (s, 2H), 3.89 (s, 2H), 2.22 (d, A of AB, J_{AB} = 15.1 Hz, 2H), 2.16 (d, B of AB, J_{AB} = 15.2 Hz, 2H), 1.46-1.43 (m, 2H), 1.26 (s, 2H), 1.20 (s, 9H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.73 (e), 129.03 (o), 69.84 (e), 44.66 (e), 41.75 (e), 40.58 (e), 39.02 (e), 27.28 (o), 17.92 (e), 15.02 (o).

IR (Neat) 3057 (w), 2974 (w), 2907 (w), 2848 (w), 1730 (vs), 1639 (w), 1480 (m), 1282 (s), 1156 (vs), 914 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{25}O_2$ 225.1849, found 225.1844.



(1-(4-Methoxyphenyl)cyclopent-3-enyl)methyl pivalate 173d.

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 90:10). mp = 36-38 °C.

Representative Experimental Procedure: Prepared in accordance to **173a** using methyl 1-(4-methoxyphenyl)cyclopent-3-enecarboxylate **172d** (2.32 g, 10 mmol) in 92%.

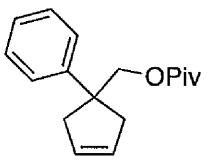
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H),

5.74 (s, 2H), 4.05 (s, 2H), 3.79 (s, 3H), 2.74-2.66 (m, 4H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.57 (e), 157.88 (e), 139.04 (e), 129.26 (o), 128.18 (o), 113.46 (o), 71.43 (e), 55.32 (o), 49.37 (e), 42.60 (e), 38.91 (e), 27.23 (o).

IR (Neat) 3054 (w), 2957 (w), 2933 (w), 2910 (w), 2835 (w), 1723 (s), 1610 (m), 1513 (s), 1478 (m), 1459 (m), 1268 (m), 1246 (s), 1184 (s), 1144 (vs), 1033 (s), 835 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{24}O_3Na$ 311.1623, found 311.1629.



(1-Phenylcyclopent-3-enyl)methyl pivalate 173e.

Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

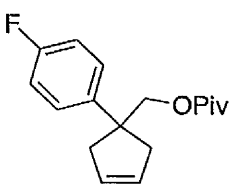
Representative Experimental Procedure: Prepared in accordance to **173a** using methyl 1-phenylcyclopent-3-enecarboxylate **172e** (2.02 g, 10 mmol) in 93%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 7.20 (t, J = 8.8 Hz, 1H), 5.75 (s, 2H), 4.08 (s, 2H), 2.77 (d, A of AB, J_{AB} = 14.7 Hz, 2H), 2.70 (d, B of AB, J_{AB} = 14.6 Hz, 2H), 1.09 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.53 (e), 146.88 (e), 129.23 (o), 128.15 (o), 127.22 (o), 126.17 (o), 71.34 (e), 50.02 (e), 42.45 (e), 38.92 (e), 27.15 (o).

IR (Neat) 3059 (w), 2972 (w), 1727 (vs), 1602 (w), 1480 (m), 1283 (m), 1150 (vs), 1034 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{22}O_2Na$ 281.1517, found 281.1522.



(1-(4-Fluorophenyl)cyclopent-3-enyl)methyl pivalate 173f.

Colour and state: Colorless oil. R_f = 0.3 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: Prepared in accordance to **173a** using

methyl 1-(4-fluorophenyl)cyclopent-3-enecarboxylate **172f** (2.20 g, 10 mmol) in 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 7.01-6.96 (m, J = 8.8 Hz, 2H), 5.75 (s, 2H), 4.05 (s, 2H), 2.74-2.67 (m, 4H), 1.09 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.46 (e), 161.36 (e, d, $J_{C\text{-}F}$ = 244.3 Hz, CF), 142.58 (e, d, $J_{C\text{-}F}$ = 3.5 Hz, CCCCF), 129.24 (o), 128.72 (o, d, $J_{C\text{-}F}$ = 7.9 Hz, CCCF), 114.84 (o, d, $J_{C\text{-}F}$ = 21.1 Hz, CCF), 71.24 (e), 49.65 (e), 42.53 (e), 38.92 (e), 27.22 (o).

IR (Neat) 3059 (w), 2972 (w), 1727 (vs), 1604 (w), 1512 (s), 1480 (m), 1283 (s), 1232 (m), 1153 (s), 835 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{21}O_2Na$ 299.1423, found 299.1429.

***tert*-Butyldimethyl(1-methylcyclopent-3-enyloxy)silane 174a.**[134]

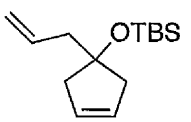
Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: Ethyl acetate (0.98 mL, 10 mmol) was added dropwise to a solution of allylmagnesium bromide (1.0 M in diethyl ether, 25 mL, 25 mmol) in tetrahydrofuran (50 mL) at 0 °C. The reaction was slowly warmed to room temperature over 4 hours, and quenched carefully with water (50 mL). The biphasic mixture was extracted three times with diethyl ether (75 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. The crude alcohol was added to a solution of 2nd Generation Grubb's catalyst (0.21 g, 2.5 mol %) in dichloromethane (100 mL). The reaction mixture was stirred for 2 hours, followed by the addition of dimethylsulfoxide (1.78 mL, 25 mmol), and then stirred for 12 hours. The crude mixture was concentrated *in vacuo* and purification by flash chromatography (silica, 10-20% ethyl acetate/hexane) furnished the cyclopentenol. The cyclopentenol was added to a solution of diisopropylethylamine (3.48 mL, 20 mmol) in

dichloromethane (50 mL) at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (3.44 mL, 15 mmol) was added dropwise to the resulting mixture and stirred for 2 hours at 0 °C. The reaction was quenched with water (100 mL), extracted three times with diethyl ether (75 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane) furnished cyclopentene **174a** in 65%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 2H), 2.49 (d, A of AB, J_{AB} = 15.1 Hz, 2H), 2.32 (d, B of AB, J_{AB} = 14.8 Hz, 2H), 1.36 (s, 3H), 0.85 (s, 9H), 0.06 (s, 6H).

IR (Neat) 3060 (w), 2957 (w), 2857 (w), 2929 (m), 1473 (w), 1463 (w), 1370 (w), 1308 (w), 1250 (s), 1155 (m), 1085 (m), 1027 (s), 834 (s), 772 (s) cm^{-1}.



(1-Allylcyclopent-3-enyloxy)(*tert*-butyl)dimethylsilane 174b.

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

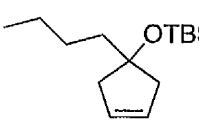
Representative Experimental Procedure: Prepared in accordance to **174a** using methyl but-3-enoate (1.00 g, 10 mmol) in 60%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92-5.84 (m, 1H), 5.62 (s, 2H), 5.05-5.02 (m, 2H), 2.45-2.37 (m, 4H), 2.35 (d, J = 7.4 Hz, 2H), 0.85 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.69 (o), 128.88 (o), 116.99 (e), 83.21 (e), 47.77 (e), 46.61 (e), 25.98 (o), 18.32 (e), -2.66 (o).

IR (Neat) 3060 (w), 2955 (w), 2929 (m), 2897 (w), 2857 (m), 1640 (w), 1472 (w), 1251 (s), 1081 (s), 913 (m), 833 (s), 772 (s) cm^{-1}.

HRMS (CI, [M+]) calcd for $C_{14}H_{26}OSi$ 238.1747, found 238.1744.



***tert*-Butyl(1-butylcyclopent-3-enyloxy)dimethylsilane 174c.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: Prepared in accordance to **174a** using

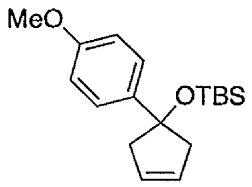
methyl pentanoate (1.16 g, 10 mmol) in 64%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (s, 2H), 2.38-2.40 (m, 4H), 1.59-1.56 (m, 2H), 1.39-1.26 (m, 4H), 0.90 (t, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 128.95 (o), 83.85 (e), 47.06 (e), 43.15 (e), 26.99 (e), 25.86 (o), 23.41 (e), 18.37 (e), 14.33 (o), -2.73 (o).

IR (Neat) 2955 (m), 2929 (m), 2857 (m), 1472 (m), 1361 (w), 1252 (s), 1053 (s), 1005 (m), 835 (s), 780 (s) cm^{-1}.

HRMS (CI, [M+]) calcd for $C_{15}H_{30}OSi$ 254.2055, found 254.2060.



***tert*-Butyl(1-(4-methoxyphenyl)cyclopent-3-enyloxy) dimethylsilane 174d.**

Colour and state: Colorless oil. R_f = 0.4 (100% Hexane).

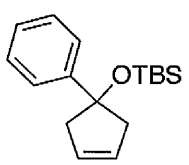
Representative Experimental Procedure: Prepared in accordance to **174a** using methyl 4-methoxybenzoate (1.66 g, 10 mmol) in 69%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.75 (s, 2H), 3.80 (s, 3H), 2.84-2.76 (m, 4H), 0.89 (s, 9H), -0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.22 (e), 141.52 (e), 128.85 (o), 126.54 (o), 113.21 (o), 84.22 (e), 55.37 (o), 50.18 (e), 26.10 (o), 18.49 (e), -2.93 (o).

IR (Neat) 3059 (w), 2953 (m), 2929 (m), 2855 (m), 1612 (m), 1582 (w), 1512 (s), 1463 (m) 1311 (w), 1247 (vs), 1179 (m), 1085 (s), 1041 (m), 996 (m), 834 (s), 774 (s) cm^{-1}.

HRMS (CI, $[M+Na]^+$) calcd for $C_{18}H_{28}O_2NaSi$ 327.1756, found 327.1764.



***tert*-Butyldimethyl(1-phenylcyclopent-3-enyloxy)silane 174e.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: Prepared in accordance to

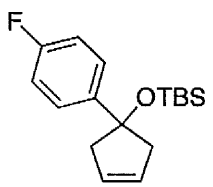
174a using methyl benzoate (1.36 g, 10 mmol) in 68%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 5.77 (s, 2H), 2.86 (d, A of AB, J_{AB} = 16.1 Hz, 2H), 2.81 (d, B of AB, J_{AB} = 16.6 Hz, 2H), 0.91 (s, 9H), -0.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.53 (e), 128.81 (o), 127.94 (o), 126.42 (o), 125.22 (o), 84.39 (e), 50.59 (e), 26.11 (o), 18.54 (e), -2.92 (o).

IR (Neat) 3059 (w), 2954 (m), 2928 (m), 2856 (m), 1601 (w), 1462 (w), 1254 (s), 1072 (s), 995 (m), 833 (s), 773 (s), 699 (s) cm^{-1}.

HRMS (CI, [M+]) calcd for $C_{17}H_{26}O_1Si$ 274.1747, found 274.1746.



***tert*-Butyl(1-(4-fluorophenyl)cyclopent-3-enyloxy)dimethyl silane 173f.**

Colour and state: Colorless oil. R_f = 0.6 (100% Hexane).

Representative Experimental Procedure: Prepared in accordance to **174a** using methyl 4-fluorobenzoate (1.54 g, 10 mmol) in 66%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.00-6.95 (m, J = 8.8 Hz, 2H), 5.76 (s, 2H), 2.80 (s, 4H), 0.90 (s, 9H), -0.02 (s, 6H).

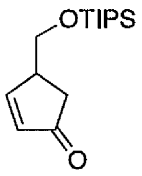
^{13}C NMR (125 MHz, $CDCl_3$) δ 161.60 (e, d, $J_{C\text{-}F}$ = 244.4 Hz, CF), 145.30 (e, d, $J_{C\text{-}F}$ = 2.8 Hz, CCCCF), 128.83 (o), 126.83 (o, d, $J_{C\text{-}F}$ = 7.6 Hz, CCCF), 114.58 (o, d, $J_{C\text{-}F}$ = 21.1 Hz, CCF), 84.09 (e), 50.43 (e), 26.08 (o), 18.49 (e), -2.92 (o).

IR (Neat) 3060 (w), 2955 (m), 2929 (m), 2856 (m), 1602 (w), 1508 (s), 1472 (w), 1231 (s), 1253 (m), 1157 (m), 1085 (s), 995 (m), 832 (s), 774 (s) cm^{-1}.

General Procedure for the Copper(I)-NHC-Catalyzed Allylic Oxidation of Cyclopentenes:

Copper(I)-NHC catalyst **183** (5.04 mg, 0.013 mmol) and sodium bicarbonate

(21 mg, 0.25 mmol) were added to a 10 mL round bottom flask under air. *The septa contained a needle to allow gas to escape during the course of the reaction.* Acetonitrile (0.50 mL) was added to reaction flask, followed by the cyclopentene **171, 172a-f, 173a-f, 174a-f** or **218** (0.25 mmol) and stirred for *ca.* 10 minutes. *tert*-Butylhydroperoxide (5.5 M in decane, 0.23 mL, 1.25 mmol) was added to the reaction solution *via* syringe-pump (rate of *ca.* 0.3 eq/h) at room temperature and stirred until completion (t.l.c. control). The solution was filtered through a short plug of silica using ethyl acetate and concentrated *in vacuo*. The crude oils were purified by flash chromatography (silica, eluting with ethyl acetate/hexanes) to afford the cyclopentenones.



4-(((Triisopropylsilyl)oxy)methyl)cyclopent-2-enone 179.[144]

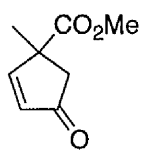
Colour and state: Colorless oil. *Regioselectivity:* ***179/180*** = 3:1.

R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **171** (0.064 g, 0.25 mmol) in 59%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 5.7, 2.5 Hz, 1H), 6.19 (dd, J = 5.7, 2.0 Hz, 1H), 3.83 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 5.7 Hz, 1H), 3.68 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 6.8 Hz, 1H), 3.16-3.10 (m, 1H), 2.42 (dd, A of ABX, J_{AB} = 18.7 Hz, J_{AX} = 6.6 Hz, 1H), 2.13 (dd, B of ABX, J_{AB} = 18.8 Hz, J_{BX} = 2.3 Hz, 1H), 1.05-1.00 (m, 21H).

IR (Neat) 2943 (w), 2866 (m), 1718 (vs), 1464 (w), 1097 (s) cm^{-1}.



Methyl 1-methyl-4-oxocyclopent-2-enecarboxylate 186a.

Colour and state: Colorless oil; *Regioselectivity:* ***186a/187a*** = 10:1.

R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

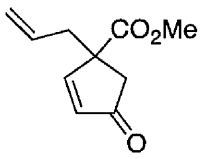
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **172a** (0.035 g, 0.25 mmol) in 77%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 5.7 Hz, 1H), 6.15 (d, J = 5.7 Hz, 1H), 3.73 (s, 3H), 2.98 (d, A of AB, J_{AB} = 18.9 Hz, 1H), 2.25 (d, B of AB, J_{AB} = 18.8 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.75 (e), 174.10 (e), 165.97 (o), 133.18 (o), 52.88 (o), 45.80 (e), 42.80 (e), 24.82 (o).

IR (Neat) 2918 (m), 2850 (w), 1719 (s), 1591 (w), 1458 (w), 1280 (m), 1195 (m), 1171 (m), 808 (m) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_8H_{14}O_3N$ 172.0968, found 172.0970.



Methyl 1-allyl-4-oxocyclopent-2-enecarboxylate 186b.

Colour and state: Colorless oil; *Regioselectivity:* ***186b/187b*** = 14:1.

R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

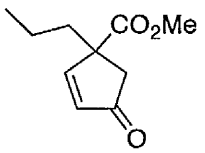
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **172b** (0.042 g, 0.25 mmol) in 74%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 5.7 Hz, 1H), 6.17 (d, J = 5.7 Hz, 1H), 5.63 (ddt, J = 17.3, 10.0, 7.2 Hz, 1H), 5.14-5.10 (m, 2H), 3.73 (s, 3H), 2.90 (d, A of AB, J_{AB} = 18.8 Hz, 1H), 2.60 (dd, A of ABX, J_{AB} = 13.8 Hz, J_{AX} = 7.8 Hz, 1H), 2.52 (dd, B of ABX, J_{AB} = 13.8 Hz, J_{BX} = 6.9 Hz, 1H), 2.34 (d, B of AB, J_{AB} = 18.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.27 (e), 164.33 (o), 134.11 (o), 131.93 (o), 120.12 (e), 55.60 (e), 52.84 (o), 42.94 (e), 42.13 (e).

IR (Neat) 2955 (w), 1717 (vs), 1591 (w), 1436 (m), 1218 (m), 1192 (m), 926 (m), 807 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{10}H_{13}O_3$ 181.0859, found 181.0855.



Methyl 4-oxo-1-propylcyclopent-2-enecarboxylate 186c.

Colour and state: Colorless oil; *Regioselectivity:* ***186c/187c*** = 16:1.

R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

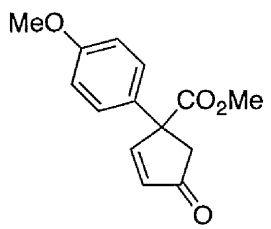
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **172c** (0.042 g, 0.25 mmol) in 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 5.7 Hz, 1H), 6.14 (d, J = 5.7 Hz, 1H), 3.73 (s, 3H), 2.95 (d, A of AB, J_{AB} = 18.8 Hz, 1H), 2.30 (d, B of AB, J_{AB} = 18.8 Hz, 1H), 1.90-1.84 (m, 1H), 1.72-1.66 (m, 1H), 1.31-1.23 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.65 (e), 173.57 (e), 165.22 (o), 133.40 (o), 56.07 (e), 52.72 (o), 43.58 (e), 40.59 (e), 18.76 (e), 14.29 (o).

IR (Neat) 2959 (w), 2875 (w), 1717 (vs), 1591 (w), 1435 (w), 1224 (m), 1192 (m), 1163 (s), 806 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{10}H_{15}O_3$ 183.1016, found 183.1011.



Methyl 1-(4-methoxyphenyl)-4-oxocyclopent-2-ene carboxylate 186d.

Colour and state: Colorless solid; *Regioselectivity:*

186d/187d ≥19:1. R_f = 0.3 (Hexane:Ethyl acetate = 80:20). mp = 47-49 °C.

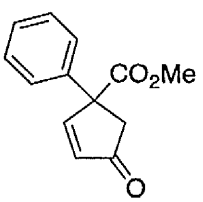
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **172d** (0.058 g, 0.25 mmol) in 82%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 5.7 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.30 (d, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.47 (d, A of AB, J_{AB} = 18.9 Hz, 1H), 2.58 (d, B of AB, J_{AB} = 18.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.30 (e), 172.68 (e), 163.33 (o), 159.16 (e), 133.95 (o), 132.97 (e), 127.19 (o), 114.53 (o), 59.34 (e), 55.44 (o), 53.20 (o), 47.00 (e).

IR (Neat) 3074 (w), 2959 (w), 1715 (vs), 1508 (s), 1436 (m), 1247 (vs), 1153 (s), 1031 (s), 821 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{15}O_4$ 247.0965, found 247.0965.



Methyl 4-oxo-1-phenylcyclopent-2-enecarboxylate 186e.

Colour and state: Colorless oil; *Regioselectivity:* ***186e/187e*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

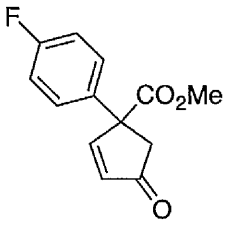
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **172e** (0.050 g, 0.25 mmol) in 84%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 5.6 Hz, 1H), 7.37 (t, J = 7.1 Hz, 2H), 7.30 (t, J = 7.1 Hz, 1H), 7.20 (d, J = 7.1 Hz, 1H), 6.33 (d, J = 5.7 Hz, 1H), 3.75 (s, 3H), 3.51 (d, A of AB, J_{AB} = 18.8 Hz, 1H), 2.59 (d, B of AB, J_{AB} = 18.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.12 (e), 172.46 (e), 163.09 (o), 140.96 (e), 134.25 (o), 129.23 (o), 127.96 (o), 126.01 (o), 60.07 (e), 53.27 (o), 46.92 (e).

IR (Neat) 3073 (w), 3013 (w), 2961 (w), 1710 (vs), 1591 (m), 1429 (s), 1239 (s), 1144 (s), 1041 (s), 817 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{13}H_{13}O_3$ 217.0859, found 217.0860.



Methyl 1-(4-fluorophenyl)-4-oxocyclopent-2-enecarboxylate 186f.

Colour and state: Colorless oil; *Regioselectivity:* ***186f/187f*** ≥19:1.

R_f = 0.3 (Hexane:Ethyl acetate = 80:20).

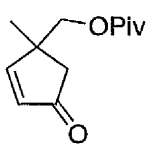
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **172f** (0.055 g, 0.25 mmol) in 84%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 5.7 Hz, 1H), 7.20-7.16 (m, 2H), 7.04 (t, J = 8.7 Hz, 2H), 6.33 (d, J = 5.6 Hz, 1H), 3.74 (s, 3H), 3.49 (d, A of AB, J_{AB} = 18.9 Hz, 1H), 2.54 (d, B of AB, J_{AB} = 18.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.74 (e), 172.29 (e), 162.65 (o), 162.22 (e, d, $J_{C\text{-}F}$ = 248.0 Hz, CF), 136.78 (e, d, $J_{C\text{-}F}$ = 3.5 Hz, CCCCF), 134.42 (o), 127.82 (o, d, $J_{C\text{-}F}$ = 8.2 Hz, CCCF), 116.12 (o, d, $J_{C\text{-}F}$ = 21.3 Hz, CCF), 59.40 (e), 53.34 (o), 46.97 (e).

IR (Neat) 2956 (w), 1718 (vs), 1601 (w), 1509 (s), 1435 (w), 1235 (s), 1151 (m), 1039 (m), 837 (m).

HRMS (CI, $[M+H]^+$) calcd for $C_{13}H_{12}O_3F$ 235.0765, found 235.0766.



(1-Methyl-4-oxocyclopent-2-enyl)methyl pivalate 181a.

Colour and state: Colorless oil; *Regioselectivity:* ***181a/182a*** = 18:1.

R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

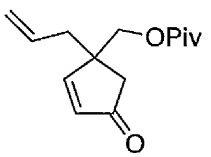
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **173a** (0.049 g, 0.25 mmol) in 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 5.7 Hz, 1H), 6.11 (d, J = 5.5 Hz, 1H), 4.14 (d, A of AB, J_{AB} = 10.8 Hz, 1H), 3.92 (d, B of AB, J_{AB} = 10.6 Hz, 1H), 2.41 (d, A of AB, J_{AB} = 18.5 Hz, 1H), 2.14 (d, B of AB, J_{AB} = 18.3 Hz, 1H), 1.25 (s, 3H), 1.14 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.58 (e), 178.23 (e), 168.68 (o), 133.73 (o), 68.73 (e), 45.67 (e), 45.39 (e), 39.00 (e), 27.20 (o), 23.02 (o).

IR (Neat) 2971 (w), 2875 (w), 1714 (vs), 1588 (w), 1481 (w), 1282 (m), 1144 (s), 798 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{12}H_{19}O_3$ 211.1329, found 211.1328.



(1-Allyl-4-oxocyclopent-2-enyl)methyl pivalate 181b.

Colour and state: Colorless oil; *Regioselectivity:* ***181b/182b*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

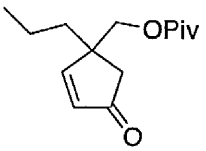
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **173b** (0.056 g, 0.25 mmol) in 77%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 5.7 Hz, 1H), 6.18 (d, J = 5.6 Hz, 1H), 5.66 (ddt, J = 16.9, 10.0, 7.5 Hz, 1H), 5.16-5.11 (m, 2H), 4.19 (d, A of AB, J_{AB} = 10.9 Hz, 1H), 3.97 (d, B of AB, J_{AB} = 11.1 Hz, 1H), 2.35-2.32 (m, 2H), 2.30-2.27 (m, 2H), 1.16 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.14 (e), 178.23 (e), 167.09 (o), 134.84 (o), 132.07 (o), 120.07 (e), 67.64 (e), 49.04 (e), 42.86 (e), 40.23 (e), 39.09 (e), 27.24 (o).

IR (Neat) 2975 (w), 1717 (vs), 1590 (w), 1481 (w), 1281 (m), 1148 (s), 1035 (w), 994 (w), 922 (w) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{21}O_3$ 237.1485, found 237.1486.



(4-Oxo-1-propylcyclopent-2-enyl)methyl pivalate 181c.

Colour and state: Colorless oil; *Regioselectivity:* ***181c/182c*** ≥19:1. R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

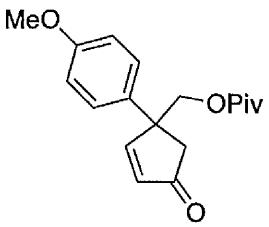
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **173c** (0.056 g, 0.25 mmol) in 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 5.7 Hz, 1H), 6.13 (d, J = 5.7 Hz, 1H), 4.18 (d, A of AB, J_{AB} = 11.0 Hz, 1H), 3.94 (d, B of AB, J_{AB} = 11.1 Hz, 1H), 2.31 (d, A of AB, J_{AB} = 18.9 Hz, 1H), 2.22 (d, B of AB, J_{AB} = 18.5 Hz, 1H), 1.60-1.48 (m, 2H), 1.35-1.10 (m, 2H), 0.93 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.66 (e), 178.29 (e), 167.99 (o), 134.26 (o), 67.80 (e), 49.36 (e), 43.29 (e), 39.02 (e), 38.01 (e), 27.21 (o), 17.75 (e), 14.69 (o).

IR (Neat) 2960 (m), 2934 (w), 2874 (w), 1715 (vs), 1590 (w), 1481 (m), 1281 (s), 1144 (vs), 1035 (w), 796 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{23}O_3$ 239.1642, found 239.1641.



(1-(4-Methoxyphenyl)-4-oxocyclopent-2-enyl)methyl pivalate 181d.

Colour and state: Colorless oil; *Regioselectivity:* ***181d/182d*** ≥19:1. R_f = 0.3 (Hexane:Ethyl acetate = 80:20).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **173d** (0.072 g, 0.25 mmol) in 85%.

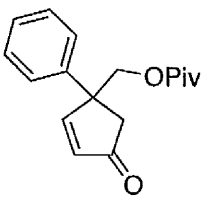
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 6.0 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.30 (d, J = 5.7 Hz, 1H), 4.47 (d, A of AB, J_{AB} = 11.0 Hz,

1H), 4.21 (d, B of AB, J_{AB} = 11.0 Hz, 1H), 3.79 (s, 3H), 2.74 (d, A of AB, J_{AB} = 18.5 Hz, 1H), 2.59 (d, B of AB, J_{AB} = 18.6 Hz, 1H), 1.11 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.07 (e), 178.18 (e), 165.91 (o), 158.91 (e), 134.34 (o), 133.38 (e), 127.50 (o), 114.41 (o), 68.30 (e), 55.42 (o), 52.32 (e), 46.72 (e), 38.98 (e), 27.16 (o).

IR (Neat) 2971 (w), 1717 (vs), 1610 (w), 1514 (s), 1480 (w), 1280 (m), 1252 (s), 1141 (s), 1035 (m), 969 (w), 832 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{22}O_4Na$ 325.1416, found 325.1425.



(4-Oxo-1-phenylcyclopent-2-enyl)methyl pivalate 181e.

Colour and state: Colorless oil; *Regioselectivity:* ***181e/182e*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

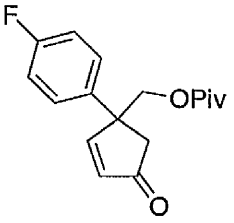
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **173e** (0.065 g, 0.25 mmol) in 84%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 5.7 Hz, 1H), 7.39-7.26 (m, 5H), 6.34 (d, J = 5.6 Hz, 1H), 4.54 (d, A of AB, J_{AB} = 10.9 Hz, 1H), 4.26 (d, B of AB, J_{AB} = 11.1 Hz, 1H), 2.78 (d, A of AB, J_{AB} = 18.2 Hz, 1H), 2.64 (d, B of AB, J_{AB} = 18.6 Hz, 1H), 1.12 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.83 (e), 178.15 (e), 165.64 (o), 141.43 (e), 134.56 (o), 129.10 (o), 127.67 (o), 126.43 (o), 68.28 (e), 52.93 (e), 46.60 (e), 38.97 (e), 27.14 (o).

IR (Neat) 2972 (w), 1717 (vs), 1593 (w), 1480 (w), 1281 (m), 1141 (s), 1036 (w), 969 (w), 762 (m), 700 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{20}O_3Na$ 295.1310, found 295.1319.



(1-(4-Fluorophenyl)-4-oxocyclopent-2-enyl)methyl pivalate 181f.

Colour and state: Colorless oil; *Regioselectivity:* ***181f/182f*** ≥19:1.

R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

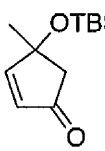
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **173f** (0.069 g, 0.25 mmol) in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 6.0 Hz, 1H), 7.24-7.20 (m, 2H), 7.05 (t, J = 8.5 Hz, 2H), 6.33 (d, J = 5.7 Hz, 1H), 4.48 (d, A of AB, J_{AB} = 11.1 Hz, 1H), 4.21 (d, B of AB, J_{AB} = 11.0 Hz, 1H), 2.75 (d, A of AB, J_{AB} = 18.1 Hz, 1H), 2.57 (d, B of AB, J_{AB} = 18.5 Hz, 1H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.40 (e), 178.07 (e), 165.22 (o), 162.02 (e, d, $J_{C\text{-}F}$ = 247.4 Hz, CF), 137.30 (e, d, $J_{C\text{-}F}$ = 3.0 Hz, CCCCF), 134.72 (o), 128.11 (o, d, $J_{C\text{-}F}$ = 8.2 Hz, CCCF), 115.98 (o, d, $J_{C\text{-}F}$ = 21.6 Hz, CCF), 68.27 (e), 52.40 (e), 46.69 (e), 38.97 (e), 27.13 (o).

IR (Neat) 2974 (w), 1717 (vs), 1604 (w), 1511 (s), 1480 (m), 1280 (m), 1230 (m), 1138 (s), 971 (w), 835 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{19}O_3FNa$ 313.1216, found 313.1226.



4-(*tert*-Butyldimethylsilyloxy)-4-methylcyclopent-2-enone 188a.

Colour and state: Colorless oil; *Regioselectivity:* ***188a/189a*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

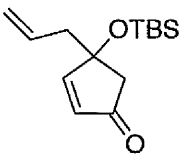
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **174a** (0.053 g, 0.25 mmol) in 72%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 5.7 Hz, 1H), 6.04 (d, J = 5.4 Hz, 1H), 2.54 (d, A of AB, J_{AB} = 18.2 Hz, 1H), 2.46 (d, B of AB, J_{AB} = 18.2 Hz, 1H), 1.49 (s, 3H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.36 (e), 167.90 (o), 132.00 (o), 78.42 (e), 51.61 (e), 29.13 (o), 25.69 (o), 17.98 (e), -2.28 (o), -2.35 (o).

IR (Neat) 2956 (w), 2930 (w), 2888 (w), 2858 (w), 1721 (vs), 1592 (w), 1473 (w), 1253 (s), 1202 (m), 1077 (s), 1018 (m), 844 (vs), 774 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{12}H_{22}O_2NaSi$ 249.1287, found 249.1291.



4-Allyl-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enone 188b.

Colour and state: Colorless oil; *Regioselectivity:* ***188b/189b*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

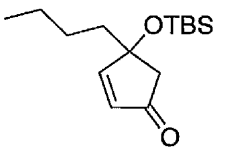
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **174b** (0.060 g, 0.25 mmol) in 70%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 5.7 Hz, 1H), 6.12 (d, J = 5.7 Hz, 1H), 5.78 (ddt, J = 17.3, 10.1, 7.1 Hz, 1H), 5.13-5.07 (m, 2H), 2.55 (d, A of AB, J_{AB} = 18.5 Hz, 1H), 2.46-2.44 (m, 2H), 2.42 (d, B of AB, J_{AB} = 18.6 Hz, 1H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.72 (e), 166.47 (o), 133.38 (o), 132.95 (o), 119.18 (e), 80.64 (e), 48.91 (e), 46.57 (e), 25.71 (o), 18.15 (e), -2.21 (o), -2.49 (o).

IR (Neat) 2955 (w), 2930 (w), 2897 (w), 2858 (w), 1723 (vs), 1641 (w), 1473 (w), 1253 (m), 1188 (m), 1075 (s), 833 (vs), 805 (s), 774 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{24}O_2NaSi$ 275.1443, found 275.1454.



4-Butyl-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enone 188c.

Colour and state: Colorless oil; *Regioselectivity:* ***188c/189c*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

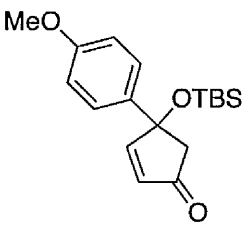
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **174c** (0.060 g, 0.25 mmol) in 75%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 5.7 Hz, 1H), 6.10 (d, J = 6.0 Hz, 1H), 2.51 (d, A of AB, J_{AB} = 18.3 Hz, 1H), 2.44 (d, B of AB, J_{AB} = 18.5 Hz, 1H), 1.73-1.59 (m, 2H), 1.37-1.18 (m, 4H), 0.94-0.82 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.21 (e), 167.22 (o), 132.89 (o), 81.14 (e), 49.62 (e), 41.87 (e), 26.59 (e), 25.75 (o), 23.09 (e), 18.17 (e), 14.14 (o), -2.21 (o), -2.45 (o).

IR (Neat) 2956 (m), 2930 (m), 2858 (w), 1723 (vs), 1463 (w), 1252 (m), 1190 (m), 1077 (s), 835 (vs), 806 (s), 774 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{28}O_2NaSi$ 291.1756, found 291.1757.



4-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl) cyclopent-2-enone 188d.

Colour and state: Colorless oil; *Regioselectivity:* ***188d/189d*** ≥19:1.

R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **174d** (0.076 g, 0.25 mmol) in 81%.

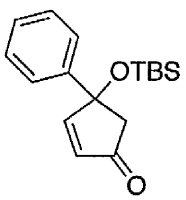
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 5.6 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.24 (d, J = 5.6 Hz, 1H), 3.80 (s, 3H) 2.83 (d, A of AB, J_{AB}

= 18.8 Hz, 1H), 2.78 (d, B of AB, J_{AB} = 18.9 Hz, 1H), 0.93 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.58 (e), 166.24 (o), 159.04 (e), 136.71 (e), 132.65 (o), 126.20 (o), 113.95 (o), 81.74 (e), 55.43 (o), 53.29 (e), 25.90 (o), 18.38 (e), -2.27 (o), -2.44 (o).

IR (Neat) 2955 (w), 2930 (w), 2857 (w), 1720 (vs), 1610 (w), 1509 (s), 1463 (w), 1249 (s), 1176 (m), 1079 (m), 932 (m), 831 (s), 806 (s), 775 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{26}O_3NaSi$ 341.1549, found 341.1550.



4-(*tert*-Butyldimethylsilyloxy)-4-phenylcyclopent-2-enone 188e.

Colour and state: Colorless oil; *Regioselectivity:* ***188e/189e*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

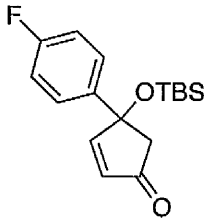
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **174e** (0.069 g, 0.25 mmol) in 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 5.7 Hz, 1H), 7.38-7.26 (m, 5H), 6.28 (d, J = 5.6 Hz, 1H), 2.84 (d, A of AB, J_{AB} = 18.8 Hz, 1H), 2.80 (d, B of AB, J_{AB} = 18.9 Hz, 1H), 0.95 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.51 (e), 166.09 (o), 144.67 (e), 133.04 (o), 128.64 (o), 127.57 (o), 124.89 (o), 82.02 (e), 53.33 (e), 25.90 (o), 18.40 (e), -2.24 (o), -2.43 (o).

IR (Neat) 2956 (w), 2930 (w), 2887 (w), 2857 (w), 1720 (vs), 1590 (w), 1472 (w), 1253 (m), 1153 (m), 1069 (s), 934 (m), 834 (s), 775 (s) 699 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{24}O_2NaSi$ 311.1443, found 311.1443.



4-(*tert*-Butyldimethylsilyloxy)-4-(4-fluorophenyl)cyclopent-2-enone 188f.

Colour and state: Colorless oil; *Regioselectivity:* ***188f/189f*** ≥19:1.

R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

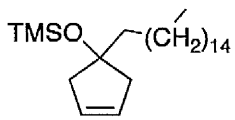
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes using **174f** (0.073 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 5.7 Hz, 1H), 7.34-7.31 (m, 2H), 7.03 (t, J = 8.6 Hz, 2H), 6.28 (d, J = 5.7 Hz, 1H), 2.83 (d, A of AB, J_{AB} = 18.9 Hz, 1H), 2.75 (d, B of AB, J_{AB} = 18.6 Hz, 1H), 0.94 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.06 (e), 165.68 (o), 162.18 (e, d, $J_{C\text{-}F}$ = 246.3 Hz, CF), 140.58 (e), 133.25 (o), 126.64 (o, d, $J_{C\text{-}F}$ = 8.2 Hz, CCCF), 115.46 (o, d, $J_{C\text{-}F}$ = 21.3 Hz, CCF), 81.74 (e), 53.34 (e), 25.89 (o), 18.37 (e), -2.23 (o), -2.42 (o).

IR (Neat) 2956 (w), 2931 (w), 2858 (w), 1721 (vs), 1602 (w), 1508 (s), 1254 (m), 1227 (s), 1156 (m), 1080 (s), 931 (m), 834 (vs), 775 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{23}O_2FNaSi$ 329.1349, found 329.1364.



(1-Heptadecylcyclopent-3-enyloxy)trimethylsilane 218.

Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

Hoveyda-Grubbs 2 catalyst (0.16 g, 2.5 mol %) was added to anhydrous dichloromethane (100 mL) under nitrogen atmosphere at room temperature. Alcohol **219** (2.92 g, 10 mmol) was added to the resultant solution dropwise and stirred until completion (t.l.c. control). Diisopropylethylamine (2.61 mL, 15 mmol) was added to the crude reaction at 0 °C and stirred for *ca.* 10 minutes. Trimethylsilyl trifluoromethanesulfonate (2.17 mL, 12 mmol) was added dropwise to the reaction

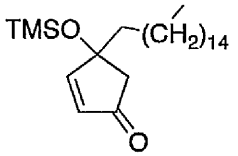
dropwise and stirred at 0 °C for 1 hour. The reaction was quenched with water (100 mL) and extracted three times with diethyl ether (100 mL). The organic extracts were washed with sat. aqueous ammonium chloride (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (silica, eluting with hexanes) afforded the cyclopentene **218** in 91%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (s, 2H), 2.44 (d, A of AB, J_{AB} = 15.7 Hz, 1H), 2.37 (d, B of AB, J_{AB} = 15.7 Hz, 1H), 1.59-1.54 (m, 2H), 1.20-140 (m, 30H), 0.88 (t, J = 6.9 Hz, 3H), 0.08 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 128.95 (o), 47.03 (e), 43.18 (e), 32.09 (e), 30.33 (e), 29.86 (e), 29.83 (e), 29.53 (e), 24.77 (e), 22.85 (e), 14.28 (o), 2.22 (o).

IR (Neat) 2922 (s), 2853 (m), 1466 (w), 1316 (w), 1249 (s), 1063 (m), 837 (s), 752 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{48}ONaSi$ 403.3372, found 403.3392.



4-Heptadecyl-4-(trimethylsilyloxy)cyclopent-2-enone 217.[135]

Colour and state: Colorless oil. *Regioselectivity* ≥19:1.

R_f = 0.4 (Hexane:Ethyl acetate = 95:5).

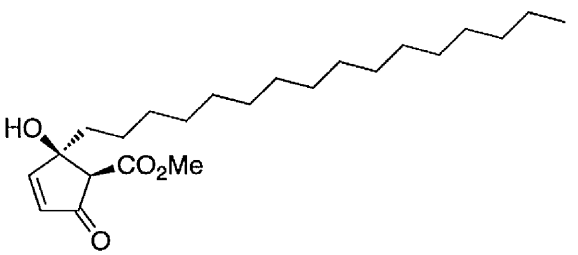
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclopentenes, modified with propionitrile (10 mL, 0.1 M) using **218** (0.38 g, 1 mmol) in 69%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 5.7 Hz, 1H), 6.10 (d, J = 5.7 Hz, 1H), 2.49 (m, 2H), 2.43-2.35 (m, 2H), 1.70-1.53 (m, 4 H), 1.25 (m, 26H), 0.87 (t, J = 7.0 Hz, 3H), 0.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.07 (e), 167.02 (o), 132.99 (o), 81.42 (e), 49.71 (e), 42.06 (e), 32.07 (e), 30.00 (e), 29.84 (e), 29.80 (e), 29.77 (e), 29.70 (e), 29.66 (e), 29.51 (e), 24.45 (e), 22.84 (e), 14.27 (o), 2.29 (o).

IR (Neat) 2923 (s), 2853 (m), 1725 (s), 1466 (w), 1340 (w), 1251(s), 1198 (w), 1075 (m), 839 (s), 753 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{46}O_2NaSi$ 417.3165, found 417.3160.



(±)-Untenone A 197.[135]

Colour and state: Colorless solid.

R_f = 0.3 (Hexane:Ethyl acetate = 80:20).

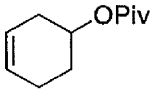
Diisopropylamine (0.09 mL, 0.70 mmol) was added to anhydrous tetrahydrofuran (2.50 mL) at 0 °C and stirred for *ca.* 10 minutes. *n*-Butyllithium (2.5 M in hexane, 0.28 mL, 0.70 mmol) was added to the resultant solution dropwise and stirred at 0 °C for 15 minutes. The solution was cooled to -78 °C and the cyclopentenone **217** (0.099 g, 0.25 mmol) in tetrahydrofuran (1 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 hour and methyl cyanoformate (0.05 mL, 0.60 mmol) in HMPA (0.25 mL) was added dropwise. The reaction was stirred at -78 °C for 1 hour and slowly warmed to room temperature. The reaction was carefully quenched with methanol (5 mL) at 0 °C and stirred vigorously for *ca.* 1 hour followed by conc. hydrochloride acid (1 drop). Water (20 mL) was added to the reaction mixture and extracted three times with ethyl acetate (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (silica, eluting with ethyl acetate/hexanes 5:1) afforded (±)-untenone A **197** in 70%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 5.6 Hz, 1H), 6.19 (d, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 1H), 3.47 (s, 1H), 1.84-1.78 (m, 1H), 1.72-1.66 (m, 1H), 1.25 (m, 30H), 0.88 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.10 (e), 169.24 (e), 167.29 (o), 132.50 (o), 80.03 (e), 60.99 (o), 53.11 (o), 40.52 (e), 32.08 (e), 29.91 (e), 29.85 (e), 29.81 (e), 29.79 (e), 29.76 (e), 29.68 (e), 29.59 (e), 29.52 (e), 28.60 (o), 24.01 (e), 22.85 (e), 14.28 (o).

IR (Neat) 3458 (b), 2917 (vs), 2850 (s), 1736 (s), 1709 (s), 1467 (w), 1436 (w), 1320 (m), 1247 (m), 1154 (m), 1002 (w), 818 (w), 766 (w), 721 (w) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}40_3O_4Na$ 403.2824, found 403.2812.



Cyclohex-3-en-1-yl pivalate 227a.[136]

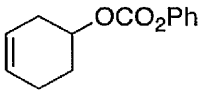
Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a solution of DMAP (0.06 g, 0.5 mmol) and triethylamine (1.04 mL, 7.5 mmol) in dichloromethane (50 mL) at 0 °C. To the reaction mixture was added trimethylacetyl chloride (0.92 mL, 7.5 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with saturated aqueous ammonium chloride (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, 2% ethyl acetate/hexane) furnished cyclohexene **227a** in 95%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69-5.65 (m, 1H), 5.58-5.54 (m, 1H), 4.50-4.95 (m, 1H), 2.37-2.31 (m, 1H), 2.20-2.01 (m, 3H), 1.85-1.79 (m, 1H), 1.75-1.68 (m, 1H),

1.17 (s, 9H).

IR (Neat) 2972 (w), 1725 (vs), 1480 (w), 1282 (s), 1157 (vs) cm^{-1}.



Cyclohex-3-en-1-yl phenyl carbonate 227b.

Colour and state: Colorless solid. R_f = 0.5 (Hexane:Ethyl acetate = 95:5). mp = 28-30 °C.

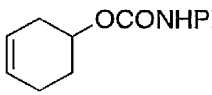
Representative Experimental Procedure: Prepared in accordance to **227a** using phenyl chloroformate (1.17 g, 7.5 mmol) in 82%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.36 (m, 2H), 7.29-7.22 (m, 1H), 7.20-7.18 (m, 2H), 5.74-5.70 (m, 1H), 5.63-5.59 (m, 1H), 5.02-4.97 (m, 1H), 2.54-2.48 (m, 1H), 2.31-2.13 (3H), 2.06-2.01 (m, 1H), 1.92-1.85 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.35 (e), 151.26 (e), 129.56 (o), 126.94 (o), 126.03 (o), 123.30 (o), 121.21 (o), 74.91 (o), 30.66 (e), 27.27 (e), 23.28 (e).

IR (Neat) 3031 (w), 2931 (w), 2848 (w), 1752 (vs), 1592 (w), 1494 (m), 1204 (vs), 1180 (vs), 1160 (vs), 994 (m) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{13}H_{18}O_3N$ 236.1281, found 236.1280.



Cyclohex-3-en-1-yl phenylcarbamate 227c.

Colour and state: Colorless solid. R_f = 0.6 (Hexane:Ethyl acetate = 90:10). mp = 78-80 °C.

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a solution of phenyl isocyanate (0.57 mL, 5.25 mmol) in tetrahydrofuran (25 mL) at 0 °C. The reaction was stirred for 16 hours at room temperature and concentrated *in vacuo*. Purification by flash chromatography (silica, 5% ethyl acetate/hexane) furnished cyclohexene **227c** in 95%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.32-7.29 (m, 2H), 7.07-7.04 (m,

1H), 6.65 (bs, 1H), 5.73-5.71 (m, 1H), 5.63-5.60 (m, 1H), 5.08-5.03 (m, 1H), 2.47-2.44 (m, 1H), 2.24-2.15 (m, 3H), 1.98-1.93 (m, 1H), 1.84-1.77 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.15 (e), 129.15 (o), 126.95 (o), 123.77 (o), 123.39 (o), 118.66 (o), 70.65 (o), 31.05 (e), 27.51 (e), 23.21 (e).

IR (Neat) 3313 (w), 2948 (w), 2918 (w), 1689 (vs), 1599 (s), 1531 (vs), 1444 (vs), 1315 (s), 1232 (vs), 1053 (s) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{13}H_{16}O_2N$ 218.1176, found 218.1176.

Cyclohex-3-en-1-yl tosylcarbamate 227d.

Colour and state: Colorless solid. R_f = 0.5 (Hexane:Ethyl acetate = 90:10). mp = 80-82 °C.

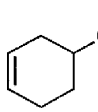
Representative Experimental Procedure: Prepared in accordance to **227c** using tosyl isocyanate in 95%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.33-7.32 (m, 2H), 5.67-5.63 (m, 1H), 5.53-5.49 (m, 1H), 4.96-4.91 (m, 1H), 2.44 (s, 3H), 2.33-2.29 (m, 1H), 2.14-1.99 (m, 3H), 1.83-1.77 (m, 1H), 1.73-1.66 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.37 (e), 145.06 (e), 135.64 (e), 129.63 (o), 128.48 (o), 126.90 (o), 123.09 (o), 73.25 (o), 30.40 (e), 26.90 (e), 22.75 (e), 21.79 (o).

IR (Neat) 3196 (w), 2937 (w), 2918 (w), 1748 (vs), 1595 (w), 1437 (s), 1339 (s), 1228 (s), 1153 (vs), 1089 (m), 1044 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{17}NO_4NaS$ 318.0776, found 318.0773.



***tert*-Butyl(cyclohex-3-en-1-yloxy)dimethylsilane 227e.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a mixture of DMAP (0.06 g, 0.5 mmol), imidazole (0.85 g, 12.5 mmol) in

dichloromethane (50 mL) at 0 °C. To the reaction mixture was added TBSCl (0.90 g, 6 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with water (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane) furnished cyclohexene **227e** in 87%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63-5.60 (m, 1H), 5.57-5.53 (m, 1H), 3.88 (dddd, J = 10.1, 8.2, 5.2, 3.1 Hz, 1H), 2.27-2.22 (m, 1H), 2.19-2.14 (m, 1H), 2.10-1.95 (m, 2H), 1.83-1.78 (m, 1H), 1.61-1.53 (m, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 126.76 (o), 124.85 (o), 68.18 (o), 35.33 (e), 31.94 (e), 26.05 (o), 24.60 (e), 18.36 (e), -4.50 (o).

IR (Neat) 2928 (m), 2857 (m), 1472 (w), 1251 (m), 1104 (vs) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{12}H_{25}OSi$ 213.1669, found 213.1664.

***tert*-Butyl(cyclohex-3-en-1-yloxy)diphenylsilane 227f.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

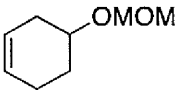
Representative Experimental Procedure: Prepared in accordance to **227e** using TBDPSCl in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.69 (m, 4H), 7.45-7.37 (m, 6H), 5.60-5.57 (m, 1H), 5.52-5.48 (m, 1H), 3.98-3.93 (m, 1H), 2.19-2.05 (m, 3H), 1.95-1.88 (m, 1H), 1.79-1.75 (m, 1H), 1.68-1.61 (m, 1H), 1.08 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.91 (o), 134.79 (e), 129.61 (o), 127.63 (o), 126.72 (o), 124.69 (o), 68.73 (o), 34.92 (e), 31.44 (e), 27.10 (o), 24.18 (e), 19.34 (e).

IR (Neat) 2929 (w), 2894 (w), 2857 (w), 1472 (w), 1427 (m), 1104 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{22}H_{28}ONaSi$ 359.1807, found 359.1810.



4-(Methoxymethoxy)cyclohex-1-ene 227g.

Colour and state: Colorless oil. R_f = 0.5 (Pentane:Diethyl ether = 90:10).

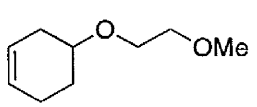
Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a mixture of diisopropylethylamine (2.61 mL, 15 mmol) at 0 °C. To the reaction mixture was added freshly distilled MOMCl (1.14 mL, 15 mmol) slowly and stirred for 6 hours at 0 °C. The reaction was quenched with water (10 mL), extracted three times with diethyl ether (20 mL) and washed with brine (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 5% diethyl ether/pentane) furnished cyclohexene **227g** in 70%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.64 (m, 1H), 5.61-5.56 (m, 1H), 4.73 (d, A of AB, J_{AB} = 6.8 Hz, 1H), 4.70 (d, B of AB, J_{AB} = 6.9 Hz, 1H), 3.86-3.81 (m, 1H), 3.38 (s, 3H), 2.39-2.34 (m, 1H), 2.21-2.16 (m, 1H), 2.12-2.04 (m, 2H), 1.94-1.89 (m, 1H), 1.69-1.62 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 126.94 (o), 124.29 (o), 94.78 (e), 72.16 (o), 55.27 (o), 32.09 (e), 28.31 (e), 23.95 (e).

IR (Neat) 2927 (w), 2886 (w), 1439 (w), 1148 (m), 1101 (m), 1034 (vs), 915 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_8H_{15}O_2$ 143.1021, found 143.1023.



4-(2-Methoxyethoxy)cyclohex-1-ene 227h.

Colour and state: Colorless oil. R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a suspension of sodium hydride (60%, 0.40 g, 10 mmol) in *N,N*-

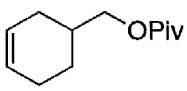
dimethylformamide (25 mL) at 0 °C and stirred for 1 hour. To the reaction mixture was added bromoethyl methyl ether (1.41 mL, 15 mmol) and stirred for 24 hours at room temperature. The reaction was quenched with water (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 10% diethyl ether/pentane) furnished cyclohexene **227h** in 46%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64-5.60 (m, 1H), 5.58-5.54 (m, 1H), 3.68-3.60 (m, 2H), 3.54 (t, J = 4.9 Hz, 2H), 3.38 (s, 3H), 2.41-2.34 (m, 1H), 2.20-2.12 (m, 1H), 2.09-1.93 (m, 3H), 1.58 (dtd, J = 13.4, 10.1, 5.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 126.94 (o), 124.44 (o), 75.19 (o), 72.42 (e), 67.40 (e), 59.22 (o), 31.81 (e), 28.02 (e), 24.37 (e).

IR (Neat) 2920 (m), 1456 (w), 1358 (w), 1199 (w), 1102 (vs), 1039 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_9H_{17}O_2$ 157.1023, found 157.1027.



Cyclohex-3-en-1-ylmethyl pivalate 231a.[140]

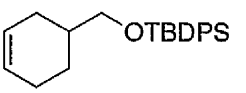
Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: 3-Cyclohexene-1-carboxylic acid (0.58 mL, 5 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.28 g, 7.5 mmol) in diethyl ether (50 mL) at 0 °C and stirred for 1 hour. The reaction was slowly quenched at 0 °C with saturated aqueous potassium sodium tartrate (50 mL) and extracted three times with diethyl ether (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude alcohol as a colourless oil. The crude alcohol was added to a solution of DMAP (0.06 g, 0.5 mmol) and triethylamine (1.39 mL, 10 mmol) in dichloromethane (50 mL) at 0 °C. To the

reaction mixture was added trimethylacetyl chloride (0.92 mL, 7.5 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with saturated aqueous ammonium chloride (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 2% ethyl acetate/hexane) furnished cyclohexene **231a** in 78%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.62 (m, 2H), 3.97-3.92 (m, 2H), 2.10-2.04 (m, 3H), 1.94-1.93 (m, 1H), 1.78-1.74 (m, 2H), 1.34-1.26 (m, 1H), 1.83 (s, 9H).

IR (Neat) 2972 (w), 2919 (w), 1729 (vs), 1480 (m), 1285 (m), 1152 (vs) cm^{-1}.



***tert*-Butyl(cyclohex-3-en-1-ylmethoxy)diphenylsilane 231b.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: 3-Cyclohexene-1-carboxylic acid (0.58 mL, 5 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.28 g, 7.5 mmol) in diethyl ether (50 mL) at 0 °C and stirred for 1 hour. The reaction was slowly quenched at 0 °C with saturated aqueous potassium sodium tartrate (50 mL) and extracted three times with diethyl ether (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude alcohol as a colourless oil. The crude alcohol was added to a solution of DMAP (0.06 g, 0.5 mmol) and imidazole (0.85 g, 12.5 mmol) in dichloromethane (50 mL) at 0 °C. To the reaction mixture was added TBDPSCl (1.95 ml, 7.5 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with water (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane)

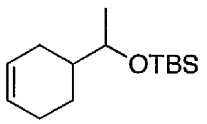
furnished cyclohexene **231b** in 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.45-7.38 (m, 6H), 5.69-5.68 (m, 2H), 3.57 (d, J = 6.1 Hz, 2H), 2.15-2.06 (m, 3H), 1.91-1.76 (m, 3H), 1.36-1.28 (m, 1H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.76 (o), 134.20 (e), 129.65 (o), 127.73 (o), 127.21 (o), 126.44 (o), 68.72 (e), 36.50 (o), 28.41 (e), 27.02 (o), 25.51 (e), 24.97 (e), 19.48 (o).

IR (Neat) 2929 (w), 2857 (w), 1472 (w), 1427 (m), 1111 (vs), 1074 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{30}ONaSi$ 373.1964, found 373.1978.



***tert*-Butyl(1-(cyclohex-3-en-1-yl)ethoxy)dimethylsilane 231c.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: 3-Cyclohexene-1-carboxylic acid (0.58 mL, 5 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.28 g, 7.5 mmol) in diethyl ether (50 mL) at 0 °C and stirred for 1 hour. The reaction was slowly quenched at 0 °C with saturated aqueous potassium sodium tartrate (50 mL) and extracted three times with diethyl ether (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude alcohol as a colourless oil. The crude alcohol was added to PDC (2.82 g, 7.5 mmol) and celite (3 g) in dichloromethane (50 mL), and stirred for 12 hours. The reaction mixture was passed through a plug of silica, washing with diethyl ether (100 mL), and concentrated *in vacuo*. The crude aldehyde was stirred in diethyl ether (50 mL) at 0 °C and methylmagnesium bromide (3 M in diethyl ether, 3.33 mL, 10 mmol) was added. The reaction was slowly warmed to room temperature over 2 hours, quenched with water (50 mL), extracted three times with diethyl ether (50 mL), and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in*

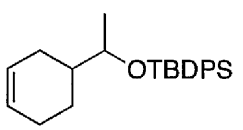
vacuo to yield a crude oil. Purification by flash chromatography (silica, eluting with 20% ethyl acetate/hexane) furnished the secondary alcohol in 75%. The alcohol (3 mmol) was added to a solution of DMAP (0.04 g, 0.3 mmol) and imidazole (0.51 g, 7.5 mmol) in dichloromethane (30 mL) at 0 °C. To the reaction mixture was added TBSCl (0.68 g, 4.5 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with water (30 ml), extracted three times with diethyl ether (50 ml) and washed with brine (100 ml). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane) furnished cyclohexene **231c** in 87%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71-5.63 (m, 2H), 3.69-3.64 (m, 1H), 2.09-1.99 (m, 3H), 1.89-1.81 (m, 1H), 1.56-1.49 (m, 1H), 1.37-1.29 (m, 1H), 1.12 (d, J = 6.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 127.07 (o), 126.92 (o), 71.99 (o), 41.67 (o), 26.91 (e), 26.06 (o), 25.70 (e), 21.25 (o), 18.25 (e), -4.10 (o), -4.64 (o).

IR (Neat) 2929 (m), 2857 (m), 1463 (w), 1373 (w), 1252 (m), 1141 (m), 1080 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{14}H_{29}OSi$ 241.1904, found 241.1905.



***tert*-Butyl(1-(cyclohex-3-en-1-yl)ethoxy)diphenylsilane 231d.**

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

Representative Experimental Procedure: 3-Cyclohexene-1-carboxylic acid (0.58 mL, 5 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.28 g, 7.5 mmol) in diethyl ether (50 mL) at 0 °C and stirred for 1 hour. The reaction was slowly quenched at 0 °C with saturated aqueous potassium sodium tartrate (50 mL) and extracted three times with diethyl ether (50 mL). The organics were dried

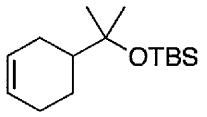
($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude alcohol as a colourless oil. The crude alcohol was added to PDC (2.82 g, 7.5 mmol) and celite (3 g) in dichloromethane (50 mL), and stirred for 12 hours. The reaction mixture was passed through a plug of silica, washing with diethyl ether (100 mL), and concentrated *in vacuo*. The crude aldehyde was stirred in diethyl ether (50 mL) at 0 °C and methylmagnesium bromide (3 M in diethyl ether, 3.33 mL, 10 mmol) was added. The reaction was slowly warmed to room temperature over 2 hours, quenched with water (50 mL), extracted three times with diethyl ether (50 mL), and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 20% ethyl acetate/hexane) furnished the secondary alcohol in 75%. The alcohol (3 mmol) was added to a solution of DMAP (0.04 g, 0.3 mmol) and imidazole (0.51 g, 7.5 mmol) in dichloromethane (30 mL) at 0 °C. To the reaction mixture was added TBDPCl (1.17 mL, 4.5 mmol) slowly and stirred for 2 hours, allowing warming up to room temperature. The reaction was quenched with water (30 ml), extracted three times with diethyl ether (50 ml) and washed with brine (100 ml). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane) furnished cyclohexene **231d** in 89%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.43-7.40 (m, 2H), 7.38-7.35 (m, 4H), 5.69-5.64 (m, 2H), 3.79-3.71 (m, 1H), 2.08-1.96 (m, 3H), 1.93-1.81 (m, 1H), 1.73-1.61 (m, 1H), 1.43-1.34 (m, 1H), 1.25-1.17 (m, 1H), 1.04 (s, 9H), 0.99 (d, J = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.10 (o), 134.51 (e), 129.61 (o), 127.63 (o), 127.48 (o), 126.93 (o), 73.10 (o), 41.58 (o), 27.22 (o), 27.09 (e), 25.85 (e), 24.95 (e), 20.31 (o), 19.61 (e).

IR (Neat) 2930 (w), 2857 (w), 1427 (m), 1109 (s), 1088 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{32}ONaSi$ 387.1964, found 387.1978.



tert-Butyl((2-(cyclohex-3-en-1-yl)propan-2-yl)oxy)dimethyl silane 231e.

Colour and state: Colorless oil. R_f = 0.8 (100% Hexane).

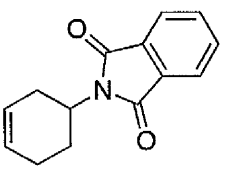
Representative Experimental Procedure: 3-Cyclohexene-1-carboxylic acid (0.58 mL, 5 mmol) was stirred in diethyl ether (25 mL) at 0 °C and methylmagnesium bromide (3 M in diethyl ether, 5 mL, 15 mmol) was added. The reaction was slowly warmed to room temperature over 2 hours, quenched with water (30 mL), extracted three times with diethyl ether (50 mL), and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the tertiary alcohol in 90%. The alcohol was added to a solution of diisopropylethylamine (1.74 mL, 10 mmol) in dichloromethane (50 mL) at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.72 mL, 7.5 mmol) was added dropwise to the resulting mixture and stirred for 2 hours at 0 °C. The reaction was quenched with water (50 mL), extracted three times with diethyl ether (75 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with hexane) furnished cyclohexene **231e** in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71-5.65 (m, 2H), 2.11-1.98 (m, 3H), 1.88-1.82 (m, 2H), 1.51-1.45 (m, 1H), 1.28-1.21 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H), 0.86 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 127.37 (o), 127.00 (o), 75.29 (e), 46.19 (o), 27.78 (o), 27.27 (o), 26.93 (e), 26.50 (e), 26.03 (o), 23.77 (e), 18.40 (e), -1.90 (o), -2.80 (o).

IR (Neat) 2955 (w), 2928 (w), 2857 (w), 1471 (w), 1365 (w), 1255 (m), 1162 (s), 1033 (vs) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{15}H_{31}OSi$ 255.2121, found 255.2121.



2-(Cyclohex-3-en-1-yl)isoindoline-1,3-dione 234a.[137]

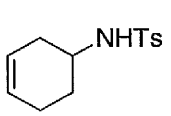
Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a solution of triphenylphosphine (1.97 g, 7.5 mmol) and phthalimide (1.10 g, 7.5 mmol) in tetrahydrofuran (50 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (1.48 mL, 7.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished cyclohexene **234a** in 61%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.82 (m, 2H), 7.71-7.70 (m, 2H), 5.73-5.66 (m, 2H), 4.41 (ddt, J = 12.0, 5.5, 3.2 Hz, 1H), 2.92 (m, 1H), 2.53 (ddt, J = 12.5, 9.7, 7.9 Hz, 1H), 2.30-2.12 (m, 3H), 1.81-1.77 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.52 (e), 133.95 (o), 132.10 (e), 126.67 (o), 125.10 (o), 123.17 (o), 47.56 (o), 28.75 (e), 26.37 (e), 25.84 (e).

IR (Neat) 3033 (w), 2947 (w), 2854 (w), 1704 (vs), 1471 (w), 1397 (m), 1373 (vs), 1330 (m), 1109 (s), 923 (m) cm^{-1}.



***N*-(Cyclohex-3-en-1-yl)-4-methylbenzenesulfonamide 234b.**

Colour and state: Colorless oil. R_f = 0.5 (Hexane:Ethyl acetate = 80:20).

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was

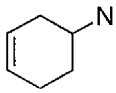
added to a solution of triphenylphosphine (1.97 g, 7.5 mmol) and *tert*-butyl tosylcarbamate (2.03 g, 7.5 mmol) in tetrahydrofuran (50 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (1.48 mL, 7.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished the *tert*-butyl tosylcarbamate cyclohexene. The cyclohexene was stirred in dichloromethane (50 mL) at 0 °C and trifluoroacetic acid (7.66 mL, 100 mmol) was added dropwise. The reaction was stirred for 4 hours, quenched with saturated aqueous sodium bicarbonate (100 mL), extracted three times with diethyl ether (75 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished cyclohexene **234b** in 45%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.76 (m, 2H), 7.31-7.29 (m, 2H), 5.66-5.61 (m, 1H), 5.51-5.47 (m, 1H), 4.50-4.49 (m, 1H), 3.52-3.45 (m, 1H), 2.43 (s, 3H), 2.22-2.18 (m, 1H), 2.10-2.00 (m, 2H), 1.86-1.79 (m, 1H), 1.76-1.71 (m, 1H), 1.55-1.49 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.22 (e), 138.28 (e), 129.70 (o), 127.00 (o), 126.95 (o), 123.98 (o), 49.04 (o), 32.37 (e), 28.87 (e), 23.54 (e), 21.55 (o).

IR (Neat) 3270 (m), 2921 (w), 1599 (w), 1438 (m), 1322 (s), 1157 (vs), 1094 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{17}NO_2Na$ 274.0878, found 274.0881.



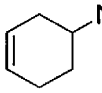
***tert*-Butyl cyclohex-3-en-1-ylcarbamate 234c.**[138]

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: Prepared in accordance to literature.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67-5.62 (m, 1H), 5.59-5.55 (m, 1H), 4.57 (bs, 1H), 3.79-3.73 (m, 1H), 2.36-2.33 (m, 1H), 2.15-2.06 (m, 2H), 1.86-1.80 (m, 2H), 1.54-1.47 (m, 1H), 1.42 (s, 9H).

IR (Neat) 3312 (m), 2947 (w), 1674 (vs), 1520 (vs), 1363 (s), 1314 (s), 1239 (s), 1167 (vs), 1022 (s) cm^{-1}.



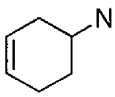
***N*-(Cyclohex-3-en-1-yl)-2,2,2-trifluoroacetamide 234d.**[138]

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: Prepared in accordance to literature.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (bs, 1H), 5.74-5.72 (m, 1H), 5.64-5.60 (m, 1H), 4.21-4.13 (m, 1H), 2.46-2.43 (m, 1H), 2.25-2.09 (m, 2H), 2.01-1.96 (m, 1H), 1.93-1.88 (m, 1H), 1.73-1.67 (m, 1H).

IR (Neat) 3292 (m), 2937 (w), 1698 (s), 1558 (m), 1180 (s), 1151 (vs) cm^{-1}.



***tert*-Butyl cyclohex-3-en-1-yl(methyl)carbamate 234e.**[139]

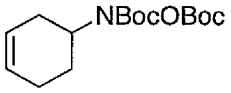
Colour and state: Colorless oil. R_f = 0.6 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: *tert*-Butyl cyclohex-3-en-1-ylcarbamate **234c** (0.59 g, 3 mmol) was added to a suspension of sodium hydride (0.18 g, 4.5 mmol) in *N,N*-dimethylformamide (30 mL) at 0 °C and stirred for 1 hour. To the reaction mixture was added iodomethane (0.28 mL, 4.5 mmol) and stirred for a further 2 hours. The reaction was quenched with water (50 mL), extracted three times with diethyl ether (50 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash

chromatography (silica, eluting with 3% ethyl acetate/hexane) furnished cyclohexene **234e** in 88%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65-5.61 (m, 2H), 4.26-4.05 (m, 1H), 2.74 (s, 3H), 2.17-2.05 (m, 4H), 1.70-1.62 (m, 2H), 1.46 (s, 9H).

IR (Neat) 2973 (w), 2922 (w), 1687 (vs), 1363 (s), 1311 (s), 1139 (vs) cm^{-1}.



***tert*-Butyl (tert-butoxycarbonyl)oxy(cyclohex-3-en-1-yl) carbamate 234f.**

Colour and state: Colorless solid. R_f = 0.6 (Hexane:Ethyl acetate = 95:5). mp = 68-71 °C.

Representative Experimental Procedure: Cyclohexenol **226** (0.49 g, 5 mmol) was added to a solution of triphenylphosphine (1.97 g, 7.5 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)oxycarbamate (1.75 g, 7.5 mmol) in tetrahydrofuran (50 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (1.48 mL, 7.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 3% ethyl acetate/hexane) furnished cyclohexene **234f** in 53%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61-5.60 (m, 2H), 4.29-4.21 (m, 1H), 2.34-2.08 (m, 4H), 1.97-1.95 (m, 1H), 1.81-1.80 (m, 1H), 1.51 (s, 9H), 1.47 (s, 9H).

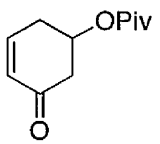
^{13}C NMR (125 MHz, $CDCl_3$) δ 154.88 (e), 152.76 (e), 126.50 (o), 125.06 (o), 84.44 (e), 82.39 (e), 55.48 (o), 28.23 (o), 28.10 (e), 27.69 (o), 27.24 (e), 25.54 (e).

IR (Neat) 2976 (w), 2936 (w), 1786 (vs), 1703 (vs), 1370 (s), 1354 (vs), 1300 (m), 1240 (vs), 1146 (vs), 1083 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{27}NO_5Na$ 336.1787, found 336.1791.

General Procedure for the Copper(I)-NHC-Catalyzed Allylic Oxidation of Cyclohexenes:

Copper(I)-NHC catalyst **183** (5.04 mg, 0.013 mmol) and sodium bicarbonate (21 mg, 0.25 mmol) were added to a 10 mL round bottom flask under air. *The septa contained a needle to allow gas to escape during the course of the reaction.* Acetonitrile (0.50 mL) was added to reaction flask, followed by the cyclohexene **227a-h, 231a-e, 234a-f, (*R*)-234a, 237, (*R*)-237, 239** or **241** (0.25 mmol) and stirred for *ca.* 10 minutes. *tert*-Butylhydroperoxide (5.5 M in decane, 0.23 mL, 1.250 mmol) was added to the reaction solution *via* syringe-pump (rate of *ca.* 0.3 eq/h) at room temperature and stirred until completion (t.l.c. control). The solution was filtered through a short plug of silica using ethyl acetate and concentrated *in vacuo*. The crude oils were purified by flash chromatography (silica, eluting with ethyl acetate/hexanes) to afford the cyclohexenones.



5-Oxocyclohex-3-en-1-yl pivalate 228a.

Colour and state: Yellow oil. *Regioselectivity:* ***228a/229a*** = 1:1.

R_f = 0.3 (Hexane:Ethyl acetate = 80:20).

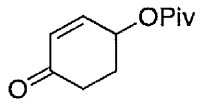
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227a** (0.046 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (dt, J = 10.1, 4.1 Hz, 1H), 6.12 (dt, J = 10.2, 2.0 Hz, 1H), 5.35-5.31 (m, 1H), 2.76-2.73 (m, 1H), 2.73 (dd, A of ABX, J_{AB} = 16.6 Hz, J_{AX} = 6.5 Hz, 1H), 2.63 (dd, B of ABX, J_{AB} = 16.6 Hz, J_{BX} = 7.2 Hz, 1H), 2.54-2.50 (m, 1H), 1.16 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.50 (e), 177.85 (e), 145.76 (o), 130.26 (o), 68.57 (o), 43.16 (e), 38.87 (e), 31.00 (e), 27.22 (o).

IR (Neat) 2973 (m), 1725 (vs), 1683 (vs), 1480 (m), 1281 (s), 1153 (vs), 1033 (s) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{11}H_{20}O_3N$ 214.1438, found 214.1440.



4-Oxocyclohex-2-en-1-yl pivalate 229a.

Colour and state: Yellow oil. *Regioselectivity:* ***228a/229a*** = 1:1.

R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

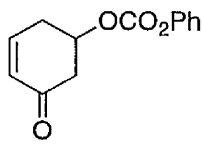
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227a** (0.046 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (ddd, *J* = 10.3, 2.8, 1.4 Hz, 1H), 6.06 (d, *J* = 10.3 Hz, 1H), 5.56-5.52 (m, 1H), 2.62 (dt, *J* = 17.0, 5.2 Hz, 1H), 2.46 (ddd, *J* = 16.9, 11.7, 5.0 Hz, 1H), 2.37-2.31 (m, 1H), 2.08 (dddd, *J* = 13.1, 11.7, 8.7, 4.5 Hz, 1H), 1.22 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.19 (e), 177.95 (e), 148.00 (o), 130.97 (o), 67.55 (o), 40.92 (e), 35.10 (e), 28.76 (e), 27.22 (o).

IR (Neat) 2973 (w), 1727 (vs), 1686 (vs), 1481 (w), 1278 (m), 1146 (vs), 1034 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{11}H_{17}O_3$ 197.1172, found 197.1171.



5-Oxocyclohex-3-en-1-yl phenyl carbonate 228b.

Colour and state: Yellow oil. *Regioselectivity:* ***228b/229b*** = 2:1.

R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

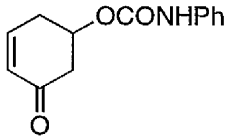
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227b** (0.055 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H), 7.30-7.27 (m, 1H), 7.21-7.19 (m, 2H), 6.96 (dt, J = 10.2, 4.1 Hz, 1H), 6.20 (dt, J = 10.2, 1.9 Hz, 1H), 5.36-5.32 (m, 1H), 2.92-2.86 (m, 1H), 2.90 (dd, A of ABX, J_{AB} = 16.8 Hz, J_{AX} = 7.9 Hz, 1H), 2.84 (dd, B of ABX, J_{AB} = 16.7 Hz, J_{BX} = 7.6 Hz, 1H), 2.77-2.70 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.67 (e), 152.96 (e), 150.91 (e), 145.42 (o), 130.49 (o), 129.68 (o), 126.36 (o), 121.05 (o), 73.40 (o), 43.10 (e), 30.89 (e).

IR (Neat) 2924 (w), 1760 (s), 1693 (s), 1488 (m), 1250 (vs), 1206 (vs) 1070 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{12}O_4Na$ 255.0633, found 255.0629.



5-Oxocyclohex-3-en-1-yl phenylcarbamate 228c.

Colour and state: Yellow oil. *Regioselectivity:* ***228c/229c*** = 2:1.

R_f = 0.4 (Hexane:Ethyl acetate = 50:50).

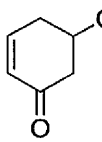
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227c** (0.054 g, 0.25 mmol) in 82%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.18-7.16 (m, 2H), 7.09-7.05 (m, 1H), 6.90 (dt, J = 10.3, 4.1 Hz, 1H), 6.64 (bs, 1H), 6.15 (dt, J = 10.2, 1.9 Hz, 1H), 5.41-5.37 (m, 1H), 2.84-2.79 (m, 1H), 2.80 (dd, A of ABX, J_{AB} = 16.6 Hz, J_{AX} = 6.9 Hz, 1H), 2.72 (dd, B of ABX, J_{AB} = 16.6 Hz, J_{BX} = 6.9 Hz, 1H), 2.68-2.62 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.68 (e), 146.05 (o), 137.62 (e), 130.25 (o), 129.23 (o), 123.82 (o), 118.80 (o), 69.78 (o), 43.46 (e), 31.32 (e).

IR (Neat) 3309 (w), 2973 (w), 1713 (s), 1673 (vs), 1599 (s), 1535 (s), 1444 (s), 1314 (m), 1209 (vs), 1050 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{13}NO_3Na$ 254.0793, found 254.0798.



5-Oxocyclohex-3-en-1-yl tosylcarbamate 228d.

Colour and state: Brown gum. *Regioselectivity:* ***228d/229d*** = 10:1.

R_f = 0.3 (Hexane:Ethyl acetate = 30:70). mp = 86-88 °C.

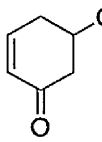
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227d** (0.074 g, 0.25 mmol) in 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.35-7.33 (m, 2H), 6.83 (dt, J = 10.1, 4.2 Hz, 1H), 6.09 (dt, J = 10.2, 1.9 Hz, 1H), 5.27-5.23 (m, 1H), 2.69-2.65 (m, 2H), 2.60-2.54 (m, 2H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.64 (e), 149.81 (e), 145.44 (o), 135.44 (e), 130.25 (o), 129.83 (o), 128.49 (o), 71.95 (o), 42.84 (e), 30.75 (e), 21.85 (o).

IR (Neat) 3261 (w), 2923 (w), 1671 (s), 1326 (s), 1155 (vs) 1090 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{15}NO_5NaS$ 332.0569, found 332.0578.



5-((*tert*-Butyldimethylsilyl)oxy)cyclohex-2-enone 228e.[141]

Colour and state: Yellow oil. *Regioselectivity:* ***228e/229e*** = 6:1.

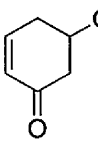
R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227e** (0.053 g, 0.25 mmol) in 75%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (ddd, J = 10.1, 5.2, 3.3 Hz, 1H), 6.05 (dt, J = 10.1, 1.9 Hz, 1H), 4.25-4.20 (m, 1H), 2.66 (dd, A of ABX, J_{AB} = 16.0 Hz, J_{AX} = 4.1 Hz, 1H), 2.49 (dd, B of ABX, J_{AB} = 16.0 Hz, J_{BX} = 9.7 Hz, 1H), 2.62-2.56 (m, 1H), 2.38 (tdd, J = 18.3, 7.7, 2.9 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 6H).

IR (Neat) 2930 (m), 2858 (w), 1680 (s), 1472 (w), 1389 (w), 1251 (s), 1099 (vs) cm^{-}

1.



5-((*tert*-Butyldiphenylsilyl)oxy)cyclohex-2-enone 228f.

Colour and state: Yellow oil. *Regioselectivity:* ***228f/229f*** = 11:1.

R_f = 0.5 (Hexane:Ethyl acetate = 90:10).

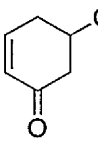
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227f** (0.084 g, 0.25 mmol) in 74%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.46-7.43 (m, 2H), 7.40-7.37 (m, 4H), 6.79 (dt, J = 10.1, 4.9 Hz, 1H), 6.03 (dt, J = 10.1, 1.9 Hz, 1H), 4.26-4.21 (m, 1H), 2.64-2.54 (m, 2H), 2.48-2.38 (m, 2H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.68 (e), 146.94 (o), 135.81 (o), 133.85 (e), 130.13 (o), 130.06 (o), 127.85 (o), 68.38 (o), 47.61 (e), 35.14 (e), 26.94 (o), 19.22 (e).

IR (Neat) 2931 (w), 2858 (w), 1682 (s), 1472 (w), 1427 (m), 1105 (vs), 1073 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{22}H_{26}O_2NaSi$ 373.1600, found 373.1608



5-(Methoxymethoxy)cyclohex-2-enone 228g.[142]

Colour and state: Yellow oil. *Regioselectivity:* ***228g/229g*** = 6:1.

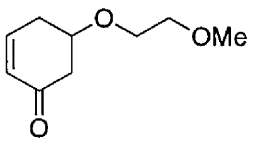
R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227g** (0.036 g, 0.25 mmol) in 73%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dt, J = 10.4, 4.2 Hz, 1H), 6.08 (d, J = 10.1, 1.9 Hz, 1H), 4.67 (bs, 2H), 4.17 (tdd, J = 8.6, 7.0, 4.3 Hz, 1H), 3.36 (s, 3H), 2.74 (dd, A of ABX, J_{AB} = 16.3 Hz, J_{AX} = 4.0 Hz, 1H), 2.60 (dd, B of ABX, J_{AB} = 16.1 Hz, J_{BX} =

8.8 Hz, 1H), 2.71-2.67 (m, 1H), 2.53-2.47 (m, 1H).

IR (Neat) 2938 (w), 1676 (s), 1389 (w), 1148 (m), 1026 (vs), 916 (m) cm^{-1}.



5-(2-Methoxyethoxy)cyclohex-2-enone 228h.

Colour and state: Yellow oil. *Regioselectivity:* ***228h/229h*** ≥19:1.

R_f = 0.3 (Hexane:Ethyl acetate = 50:50).

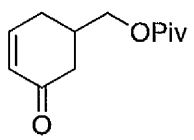
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **227h** (0.039 g, 0.25 mmol) in 75%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (ddd, J = 10.1, 5.1, 3.4 Hz, 1H), 6.06 (dt, J = 10.1, 1.9 Hz, 1H), 3.96-3.91 (m, 1H), 3.67-3.59 (m, 1H), 3.52 (t, J = 4.8 Hz, 2H), 3.37 (s, 3H), 2.79 (dd, A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.0 Hz, 1H), 2.55 (dd, B of ABX, J_{AB} = 16.1 Hz, J_{BX} = 9.7 Hz, 1H), 2.74-2.69 (m, 1H), 2.46 (tdd, J = 18.4, 7.7, 2.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.22 (e), 146.86 (o), 130.34 (o), 74.69 (o), 72.21 (e), 68.05 (e), 59.27 (o), 44.51 (e), 32.31 (e).

IR (Neat) 2923 (m), 1677 (vs), 1391 (w), 1249 (m), 1092 (vs) 1033 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_9H_{15}O_3$ 171.1016, found 171.1015.



(5-Oxocyclohex-3-en-1-yl)methyl pivalate 232a.

Colour and state: Yellow oil. *Regioselectivity:* ***232a/233a*** = 3:1.

R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

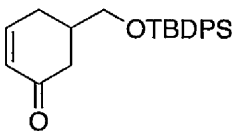
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **231a** (0.049 g, 0.25 mmol) in 78%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (ddd, J = 10.1, 5.5, 2.7 Hz, 1H), 6.06 (dd, J = 10.1, 2.7 Hz, 1H), 4.07-4.01 (m, 2H), 2.57-2.43 (m, 2H), 2.30-2.17 (m, 2H), 1.27-1.23 (m, 1H), 1.21 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.53 (e), 178.45 (e), 148.92 (o), 130.08 (o), 67.03 (e), 40.95 (e), 34.81 (o), 29.85 (e), 28.81 (e), 27.35 (o).

IR (Neat) 2973 (w), 1728 (vs), 1683 (vs), 1481 (w), 1283 (m), 1154 (vs) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{12}H_{22}O_3N$ 228.1594, found 228.1594.



5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclohex-2-enone 232b.

Colour and state: Yellow oil. *Regioselectivity:* ***232b/233b*** = 3:1.

R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

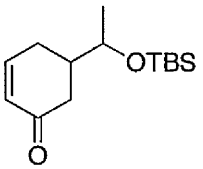
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **231b** (0.088 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.47-7.38 (m, 6H), 7.00-6.96 (m, 1H), 6.03 (d, J = 10.0 Hz, 1H), 3.67-3.57 (m, 2H), 2.53-2.28 (m, 4H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.90 (e), 149.88 (o), 135.69 (o), 133.45 (e), 129.99 (o), 129.84 (o), 127.92 (o), 66.95 (e), 41.07 (e), 37.85 (o), 28.82 (e), 26.97 (o), 19.44 (e).

IR (Neat) 2931 (w), 2858 (w), 1681 (vs), 1427 (s), 1106 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{28}O_2NaSi$ 387.1756, found 387.1757.



5-(1-((*tert*-Butyldimethylsilyl)oxy)ethyl)cyclohex-2-enone 232c.

Colour and state: Yellow oil. *Regioselectivity:* ***232c/233c*** = 7:1.

R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

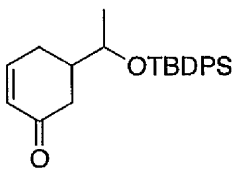
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **231c** (0.060 g, 0.25 mmol) in 74%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03-6.97 (m, 1H), 6.01 (dd, J = 10.0, 2.7 Hz, 1H), 3.78-3.68 (m, 1H), 2.46-2.23 (m, 4H), 2.10-2.04 (m, 1H), 1.35 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.52 (e), 150.47 (o), 129.59 (o), 70.50 (o), 42.84 (o), 41.93 (e), 29.05 (e), 25.98 (o), 21.28 (o), 18.18 (e), -4.04 (o).

IR (Neat) 2955 (w), 2929 (w), 2857 (w), 1683 (vs), 1388 (w), 1252 (s), 1076 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{26}O_2NaSi$ 277.1600, found 277.1604.



5-(1-((*tert*-Butyldiphenylsilyl)oxy)ethyl)cyclohex-2-enone 232d.

Colour and state: Yellow oil. *Regioselectivity: **232d/233d*** = 9:1. R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

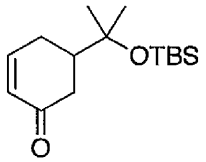
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **231d** (0.091 g, 0.25 mmol) in 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.45-7.42 (m, 2H), 7.40-7.37 (m, 4H), 7.01-6.97 (m, 1H), 6.01 (d, J = 10.0 Hz, 1H), 3.80 (tdd, J = 26.7, 10.1, 6.3 Hz, 1H), 2.48-2.23 (m, 4H), 2.16-2.09 (m, 1H), 1.05 (s, 9H), 1.03 (d, J = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.41 (e), 150.38 (o), 135.92 (o), 134.40 (e), 129.82 (o), 129.59 (o), 127.75 (o), 71.56 (o), 42.59 (o), 41.24 (e), 28.49 (e), 26.89 (o), 20.29 (o), 19.47 (e).

IR (Neat) 2931 (w), 2858 (w), 1680 (vs), 1427 (m), 1110 (vs), 1076 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{30}O_2NaSi$ 401.1913, found 401.1914.



5-(2-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)cyclohex-2-enone 232e.

Colour and state: Yellow oil. *Regioselectivity:* ***232e/233e*** = 12:1.

R_f = 0.4 (Hexane:Ethyl acetate = 90:10).

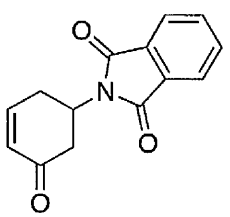
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **231e** (0.064 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04-7.00 (m, 1H), 6.01 (d, J = 10.0 Hz, 1H), 2.58-2.54 (m, 1H), 2.48-2.42 (m, 1H), 2.35-2.26 (m, 2H), 2.01-1.94 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.85 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.32 (e), 150.95 (o), 129.23 (o), 73.98 (e), 46.96 (o), 39.58 (e), 28.02 (o), 27.66 (o), 27.05 (e), 25.98 (o), 18.36 (e), -2.00 (o).

IR (Neat) 2954 (w), 2929 (w), 2857 (w), 1682 (vs), 1386 (w), 1255 (m), 1149 (s), 1033 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{28}O_2NaSi$ 291.1756, found 291.1754.



2-(5-Oxocyclohex-3-en-1-yl)isoindoline-1,3-dione 235a.

Colour and state: Colorless solid. *Regioselectivity:* ***235a/236a*** = 10:1.

R_f = 0.3 (Hexane:Ethyl acetate = 80:20). mp = 166-168 °C.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **234a** (0.057 g, 0.25 mmol) in 83%.

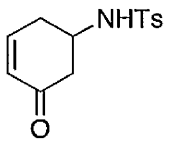
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.76-7.73 (m, 2H), 7.05-7.02 (m,

1H), 6.14 (dd, J = 10.2, 2.4 Hz, 1H), 4.83-4.76 (m, 1H), 3.44 (dd, J = 15.7, 14.3 Hz, 1H), 3.32-3.26 (m, 1H), 2.59 (d, J = 16.1, 3.9 Hz, 1H), 2.51 (dt, J = 18.1, 5.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.49 (e), 168.05 (e), 148.19 (o), 134.46 (o), 131.71 (e), 130.03 (o), 123.60 (o), 45.79 (o), 41.65 (e), 29.50 (e).

IR (Neat) 2923 (w), 1695 (vs), 1667 (vs), 1467 (w), 1375 (s), 1280 (m), 1107 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{11}NO_3Na$ 264.0637, found 264.0638.



4-Methyl-*N*-(5-oxocyclohex-3-en-1-yl)benzenesulfonamide 235b.

Colour and state: Colorless solid. *Regioselectivity:* ***235b/236b*** = 10:1. R_f = 0.3 (Hexane:Ethyl acetate = 60:40). mp = 126-130 °C.

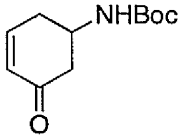
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **234b** (0.063 g, 0.25 mmol) in 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 2H), 7.31-7.29 (m, 2H), 6.85 (ddd, J = 10.1, 5.2, 3.2 Hz, 1H), 6.03 (d, J = 10.1 Hz, 1H), 5.53 (d, J = 8.0 Hz, 1H), 3.80-3.73 (m, 1H), 2.63 (dt, J = 18.5, 5.0 Hz, 1H), 2.51 (dd, A of ABX, J_{AB} = 16.3 Hz, J_{AX} = 4.3 Hz, 1H), 2.55 (dd, B of ABX, J_{AB} = 16.4 Hz, J_{BX} = 5.5 Hz, 1H), 2.43 (s, 3H), 2.39-2.34 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.94 (e), 147.54 (o), 143.95 (e), 137.57 (e), 130.05 (o), 128.63 (o), 127.02 (o), 49.39 (o), 44.86 (e), 33.34 (e), 21.70 (o).

IR (Neat) 3223 (w), 2923 (w), 1657 (vs), 1444 (w), 1330 (m), 1149 (vs), 1063 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{15}NO_3NaS$ 288.0670, found 288.0676.



***tert*-Butyl (5-oxocyclohex-3-en-1-yl)carbamate 235c.**

Colour and state: Yellow solid. *Regioselectivity:* ***235c/236c*** = 14:1. R_f = 0.3 (Hexane:Ethyl acetate = 80:20). mp = 54-57 °C.

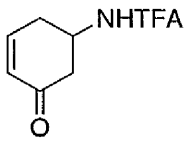
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **234c** (0.049 g, 0.25 mmol) in 72%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (ddd, J = 10.2, 4.9, 3.4 Hz, 1H), 6.09 (dt, J = 10.2, 1.9 Hz, 1H), 4.68 (bs, 1H), 4.21-4.16 (m, 1H), 2.77-2.70 (m, 2H), 2.44 (d, J = 16.1, 10.0 Hz, 1H), 2.36-2.31 (m, 1H), 1.44 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.66 (e), 154.97 (e), 147.78 (o), 130.31 (o), 79.97 (e), 46.60 (o), 44.56 (e), 32.66 (e), 28.43 (o).

IR (Neat) 3363 (w), 2975 (w), 1674 (vs), 1518 (vs), 1367 (s), 1247 (s), 1167 (vs) 1050 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{11}H_{18}O_3N$ 212.1281, found 212.1283.



2,2,2-Trifluoro-*N*-(5-oxocyclohex-3-en-1-yl)acetamide 235d.

Colour and state: Yellow oil. *Regioselectivity:* ***235d/236d*** = 14:1. R_f = 0.3 (Hexane:Ethyl acetate = 80:20).

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **234d** (0.048 g, 0.25 mmol) in 74%.

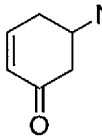
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (ddd, J = 10.2, 4.9, 3.5 Hz, 1H), 6.57 (bs, 1H), 6.16 (dt, J = 10.2, 1.9 Hz, 1H), 4.58-4.51 (m, 1H), 2.85-2.79 (m, 1H), 2.79 (dd, A of ABX, J_{AB} = 16.5 Hz, J_{AX} = 4.5 Hz, 1H), 2.57 (dd, B of ABX, J_{AB} = 16.4 Hz, J_{BX} = 9.9 Hz, 1H), 2.48 (tdd, J = 18.5, 7.9, 2.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.03 (e), 181.74 (e), 146.92 (o), 130.53 (o), 46.30

(o), 43.16 (e), 31.28 (e).

IR (Neat) 3291 (w), 2923 (w), 1706 (vs), 1683 (vs), 1554 (s), 1388 (m), 1156 (vs), 1033 (m) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_8H_{12}O_2N_2F_3$ 225.0845, found 225.0847.



***tert*-Butyl methyl(5-oxocyclohex-3-en-1-yl)carbamate 235e.**

Colour and state: Yellow oil. *Regioselectivity:* ***235e/236e*** = 16:1. R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

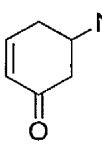
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **234e** (0.053 g, 0.25 mmol) in 69%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (ddd, J = 10.1, 6.1, 2.4 Hz, 1H), 6.06 (d, J = 10.0 Hz, 1H), 4.61-4.45 (m, 1H), 2.80 (s, 3H), 2.64-2.50 (m, 3H), 2.43 (dt, J = 18.2, 5.1 Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.61 (e), 148.67 (o), 129.99 (o), 28.55 (o).

IR (Neat) 2974 (w), 1679 (vs), 1480 (w), 1365 (s), 1146 (vs), 1033 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{12}H_{19}NO_3Na$ 248.1263, found 248.1255.



***tert*-Butyl (tert-butoxycarbonyl)oxy(5-oxocyclohex-3-en-1-yl)carbamate 235f.**

Colour and state: Pale yellow solid. *Regioselectivity:* ***235f/236f*** ≥19:1. R_f = 0.4 (Hexane:Ethyl acetate = 80:20). mp = 90-93 °C.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **234f** (0.078 g, 0.25 mmol) in 75%.

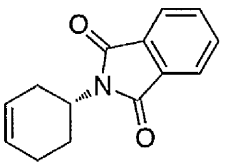
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (m, 1H), 6.06 (d, J = 9.9 Hz, 1H), 4.72-4.65 (m,

1H), 2.78-2.49 (m, 4H), 1.52 (s, 9H), 1.48 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.57 (e), 153.98 (e), 147.80 (o), 130.01 (o), 85.32 (e), 83.32 (e), 54.56 (o), 41.42 (e), 41.19 (e), 28.21 (o), 27.71 (o).

IR (Neat) 2974 (w), 1786 (vs), 1707 (vs), 1673 (vs), 1370 (s), 1237 (vs), 1147 (vs), 1095 (s), 1003 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{25}NO_6Na$ 350.1580, found 350.1577.



(*R*)-2-(Cyclohex-3-en-1-yl)isoindoline-1,3-dione (*R*)-234a.

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 90:10). $[\alpha]_D^{20}$ = +4.4 (*c* 1.00, $CHCl_3$). 99% *ee* determination by chiral HPLC: *Chiralpak AD-H* column, hexane/*i*-PrOH 95:5, 0.2 mL/min; retention times: 31.8 min (*R*). mp = 154-157 °C.

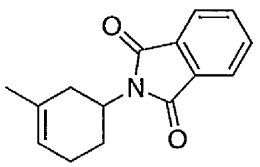
Representative Experimental Procedure: Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) oxide (10 mol %) and 4-pentenal (0.84 g, 10 mmol) was stirred in dichloromethane (100 mL) at -15 °C. To the reaction mixture was added allyltributyltin (3.41 mL, 11 mmol) and stirred at 0 °C for 12 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (100 mL), extracted three times with diethyl ether (100 mL) and washed with brine (200 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the homoallylic alcohol in 70%. The alcohol (0.63 g, 5 mmol) was added to a solution of triphenylphosphine (1.97 g, 7.5 mmol) and phthalimide (1.10 g, 7.5 mmol) in tetrahydrofuran (50 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (1.48 mL, 7.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished the

phthalimide in 55%. The oil (0.51 g, 2 mmol) was added to a solution of 2nd Generation Grubb's catalyst (0.04 g, 2.5 mol %) in dichloromethane (20 mL). The reaction mixture was stirred for 2 hours, followed by the addition of dimethylsulfoxide (0.36 mL, 5 mmol), and then stirred for 12 hours. The mixture was concentrated *in vacuo* and purification by flash chromatography (silica, 5% ethyl acetate/hexane) furnished the cyclohexene **(*R*)-234a** in 79%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.82 (m, 2H), 7.71-7.70 (m, 2H), 5.73-5.66 (m, 2H), 4.41 (ddt, J = 12.0, 5.5, 3.2 Hz, 1H), 2.92 (m, 1H), 2.53 (ddt, J = 12.5, 9.7, 7.9 Hz, 1H), 2.30-2.12 (m, 3H), 1.81-1.77 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.52 (e), 133.95 (o), 132.10 (e), 126.67 (o), 125.10 (o), 123.17 (o), 47.56 (o), 28.75 (e), 26.37 (e), 25.84 (e).

IR (Neat) 3033 (w), 2947 (w), 2854 (w), 1704 (vs), 1471 (w), 1397 (m), 1373 (vs), 1330 (m), 1109 (s), 923 (m) cm^{-1}.



2-(3-Methylcyclohex-3-en-1-yl)isoindoline-1,3-dione 237.

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 90:10). mp = 156-158 °C.

Representative Experimental Procedure: Indium (1.26 g, 11 mmol) and 4-pentenal (0.84 g, 10 mmol) was stirred in water (100 mL) at 0 °C. To the reaction mixture was added 2-methylallyl bromide (1.51 mL, 15 mmol) and stirred at room temperature for 12 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (100 mL), extracted three times with diethyl ether (100 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the homoallylic alcohol in 90%. The alcohol (0.70 g, 5 mmol) was added to a solution of triphenylphosphine (1.97 g, 7.5 mmol) and

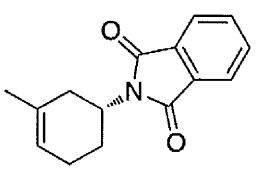
phthalimide (1.10 g, 7.5 mmol) in tetrahydrofuran (50 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (1.48 mL, 7.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished the phthalimide in 52%. The oil (0.54 g, 2 mmol) was added to a solution of 2nd Generation Grubb's catalyst (0.04 g, 2.5 mol %) in dichloromethane (20 mL). The reaction mixture was stirred for 2 hours, followed by the addition of dimethylsulfoxide (0.36 mL, 5 mmol), and then stirred for 12 hours. The mixture was concentrated *in vacuo* and purification by flash chromatography (silica, 5% ethyl acetate/hexane) furnished the cyclohexene **(*R*)-237** in 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.82 (m, 2H), 7.71-7.69 (m, 2H), 5.42 (bs, 1H), 4.44-4.37 (m, 1H), 2.86-2.80 (m, 1H), 2.48-2.40 (m, 1H), 2.19 (bs, 2H), 2.02-1.98 (m, 1H), 1.77-1.74 (m, 1H), 1.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.56 (e), 133.93 (o), 132.41 (e), 132.17 (e), 123.16 (o), 120.60 (o), 47.99 (o), 33.45 (e), 26.06 (e), 25.53 (e), 23.44 (o).

IR (Neat) 2916 (w), 1768 (w), 1706 (vs), 1374 (m), 908 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{15}NO_2Na$ 264.1000, found 264.0999.



(*R*)-2-(3-Methylcyclohex-3-en-1-yl)isoindoline-1,3-dione (*R*)-237.

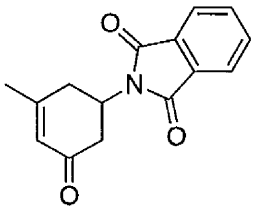
Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 90:10). $[\alpha]_D^{20}$ = -3.3 (*c* 1.00, $CHCl_3$). 94.6% *ee* determination by chiral HPLC: *Kromasil AmyCoat* column, hexane/AcOH/*i*-PrOH 99:0.1:1, 1 mL/min; retention times: 12.3 min (major), 14.2 min (minor). mp = 157-159 °C.

Representative Experimental Procedure: Bis(((*S*)-binaphthoxy)(isopropoxy)titanium)

oxide (10 mol %) and 4-pentenal (0.84 g, 10 mmol) was stirred in dichloromethane (100 mL) at -15 °C. To the reaction mixture was added 2-methylallyltributyltin (10.35 g, 30 mmol) and stirred at 0 °C for 12 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (100 mL), extracted three times with diethyl ether (100 mL) and washed with brine (200 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the homoallylic alcohol in 67%. The alcohol (0.70 g, 5 mmol) was added to a solution of triphenylphosphine (1.97 g, 7.5 mmol) and phthalimide (1.10 g, 7.5 mmol) in tetrahydrofuran (50 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (1.48 mL, 7.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished the phthalimide in 56%. The oil (0.54 g, 2 mmol) was added to a solution of 2nd Generation Grubb's catalyst (0.04 g, 2.5 mol %) in dichloromethane (20 mL). The reaction mixture was stirred for 2 hours, followed by the addition of dimethylsulfoxide (0.36 mL, 5 mmol), and then stirred for 12 hours. The mixture was concentrated *in vacuo* and purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished the cyclohexene **(*R*)-237** in 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.82 (m, 2H), 7.71-7.69 (m, 2H), 5.42 (bs, 1H), 4.44-4.37 (m, 1H), 2.86-2.80 (m, 1H), 2.48-2.40 (m, 1H), 2.19 (bs, 2H), 2.02-1.98 (m, 1H), 1.77-1.74 (m, 1H), 1.68 (s, 3H).

IR (Neat) 2916 (w), 1768 (w), 1706 (vs), 1374 (m), 908 (vs) cm^{-1}.



2-(3-Methyl-5-oxocyclohex-3-en-1-yl)isoindoline-1,3-dione 238.

Colour and state: Colorless solid. *Regioselectivity:* ≥19:1. R_f = 0.3 (Hexane:Ethyl acetate = 70:30). mp = 168-170 °C.

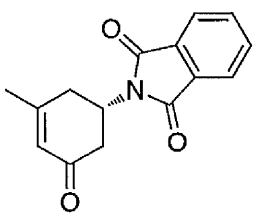
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **237** (0.060 g, 0.25 mmol) in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.85 (m, 2H), 7.75-7.74 (m, 2H), 6.00 (s, 1H), 4.78 (tdd, J = 13.7, 11.5, 4.8 Hz, 1H), 3.37-3.31 (m, 1H), 3.32-3.28 (m, 1H), 2.53 (dd, A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.3 Hz, 1H), 2.36 (dd, B of ABX, J_{AB} = 17.5 Hz, J_{BX} = 4.4 Hz, 1H), 2.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.17 (e), 168.09 (e), 160.44 (e), 134.43 (o), 131.82 (e), 126.90 (o), 123.58 (o), 45.83 (o), 40.44 (e), 34.58 (e), 24.43 (o).

IR (Neat) 2919 (w), 1770 (w), 1704 (vs), 1662 (s), 1371 (s), 1107 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{13}NO_3Na$ 278.0793, found 278.0787.



(*S*)-2-(3-Methyl-5-oxocyclohex-3-en-1-yl)isoindoline-1,3-dione (*S*)-238.

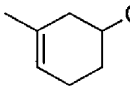
Colour and state: Colorless solid. *Regioselectivity:* ≥19:1. R_f = 0.3 (Hexane:Ethyl acetate = 70:30). $[\alpha]_D^{20}$ = +7.5 (*c* 1.00, $CHCl_3$). 91.6% *ee* determination by chiral HPLC: *Chiralpak AD-H* column, hexane/*i*-PrOH 85:15, 1 mL/min; retention times: 24.5 min (minor), 26.1 min (major). mp = 168-170 °C.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **(*R*)-237** (0.060 g, 0.25 mmol) in 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.85 (m, 2H), 7.75-7.74 (m, 2H), 6.00 (s, 1H),

4.78 (tdd, J = 13.7, 11.5, 4.8 Hz, 1H), 3.37-3.31 (m, 1H), 3.32-3.28 (m, 1H), 2.53 (dd, A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.3 Hz, 1H), 2.36 (dd, B of ABX, J_{AB} = 17.5 Hz, J_{BX} = 4.4 Hz, 1H), 2.02 (s, 3H).

IR (Neat) 2919 (w), 1770 (w), 1704 (vs), 1662 (s), 1371 (s), 1107 (m) cm^{-1}.



3-Methylcyclohex-3-en-1-yl tosylcarbamate 239.

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 85:15). mp = 83-86 °C.

Representative Experimental Procedure: Indium (1.26 g, 11 mmol) and 4-pentenal (0.84 g, 10 mmol) was stirred in water (100 mL) at 0 °C. To the reaction mixture was added 2-methylallyl bromide (1.51 mL, 15 mmol) and stirred at room temperature for 12 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (100 mL), extracted three times with diethyl ether (100 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the homoallylic alcohol in 90%. The oil (0.70 g, 5 mmol) was added to a solution of 2nd Generation Grubb's catalyst (0.11 g, 2.5 mol %) in dichloromethane (50 mL). The reaction mixture was stirred for 2 hours and was concentrated *in vacuo*. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the cyclohexenol in 70%. The cyclohexenol (0.22 g, 2 mmol) was added to a solution of tosyl isocyanate (0.34 mL, 2.2 mmol) in tetrahydrofuran (20 mL) at 0 °C. The reaction was stirred for 16 hours at room temperature and concentrated *in vacuo*. Purification by flash chromatography (silica, 10% ethyl acetate/hexane) furnished cyclohexene **239** in 85%.

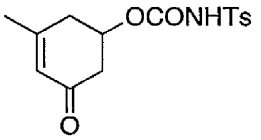
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.34-7.33 (m, 2H), 5.37-5.36 (m, 1H), 4.98-4.93 (m, 1H), 2.45 (s, 3H), 2.24-2.21 (m, 1H), 2.09-1.92 (m, 3H), 1.76-

1.71 (m, 1H), 1.69-1.64 (m, 1H), 1.62 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.31 (e), 145.06 (e), 135.75 (e), 130.41 (e), 129.67 (o), 128.50 (o), 120.80 (o), 73.81 (o), 35.13 (e), 26.66 (e), 23.39 (o), 22.50 (e), 21.81 (o).

IR (Neat) 3233 (w), 2920 (w), 1718 (s), 1441 (s), 1346 (s), 1226 (m), 1158 (vs), 1090 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{19}NO_4NaS$ 332.0932, found 332.0931.



3-Methyl-5-oxocyclohex-3-en-1-yl tosylcarbamate 240.

Colour and state: Brown solid. *Regioselectivity:* ≥19:1.

R_f = 0.3 (Hexane:Ethyl acetate = 30:70). mp = 89-92 °C.

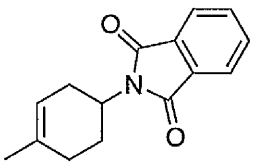
Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **239** (0.077 g, 0.25 mmol) in 79%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.35-7.33 (m, 2H), 5.94 (bs, 1H), 5.26-5.22 (m, 1H), 2.67-2.62 (m, 1H), 2.57 (dd, A of ABX, J_{AB} = 16.8 Hz, J_{AX} = 4.1 Hz, 1H), 2.36 (dd, B of ABX, J_{AB} = 10.8 Hz, J_{BX} = 4.8 Hz, 1H), 2.50-2.46 (m, 1H), 2.45 (s, 3H), 1.96 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.59 (e), 157.98 (e), 149.90 (e), 145.38 (e), 135.46 (e), 129.83 (o), 128.47 (o), 126.85 (o), 71.85 (o), 41.66 (e), 35.78 (e), 24.45 (o), 21.85 (o).

IR (Neat) 3070 (w), 1746 (s), 1658 (s), 1452 (m), 1346 (m), 1222 (m), 1161 (vs), 1090 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{17}NO_5NaS$ 346.0725, found 346.0737.



2-(4-Methylcyclohex-3-en-1-yl)isoindoline-1,3-dione 241.

Colour and state: Colorless solid. R_f = 0.4 (Hexane:Ethyl acetate = 90:10). mp = 157-160 °C.

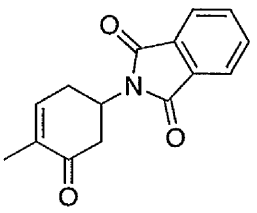
Representative Experimental Procedure: 4-Methylpent-4-enal (0.98 g, 10 mmol) was stirred in diethyl ether (100 mL) and allylmagnesium bromide (1 M in diethyl ether, 15 mL, 15 mmol) was added at 0 °C. The reaction mixture was slowly warmed to room temperature over 2 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL), extracted three times with diethyl ether (100 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (silica, eluting with 15% ethyl acetate/hexane) furnished the homoallylic alcohol in 85%. The alcohol (0.98 g, 7 mmol) was added to a solution of triphenylphosphine (2.75 g, 10.5 mmol) and phthalimide (1.54 g, 10.5 mmol) in tetrahydrofuran (70 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIAD (2.07 mL, 10.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 12 hours at room temperature and concentrated *in vacuo* onto silica. Purification by flash chromatography (silica, eluting with 5% ethyl acetate/hexane) furnished the phthalimide in 55%. The oil (0.81 g, 3 mmol) was added to a solution of 2nd Generation Grubb's catalyst (0.08 g, 2.5 mol %) in dichloromethane (30 mL). The reaction mixture was stirred for 2 hours, followed by the addition of dimethylsulfoxide (0.53 mL, 7.5 mmol), and then stirred for 12 hours. The mixture was concentrated *in vacuo* and purification by flash chromatography (silica, 5% ethyl acetate/hexane) furnished the cyclohexene **241** in 77%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.80 (m, 2H), 7.69-7.68 (m, 2H), 5.37 (bs, 1H), 4.38-4.32 (m, 1H), 2.86-2.78 (m, 1H), 2.55 (qd, J = 12.5, 5.9 Hz, 1H), 2.24-2.18 (m, 1H), 2.11-2.04 (m, 2H), 1.80-1.75 (m, 1H), 1.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.57 (e), 133.90 (o), 133.85 (e), 132.20 (e), 123.14 (o), 119.35 (o), 47.78 (o), 30.62 (e), 28.67 (e), 26.56 (e), 23.42 (o).

IR (Neat) 2960 (w), 2914 (w), 1697 (vs), 1394 (m), 1378 (s), 1108 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{15}NO_2Na$ 264.1000, found 264.0996.



2-(4-Methyl-5-oxocyclohex-3-en-1-yl)isoindoline-1,3-dione 243.

Colour and state: Colorless solid. *Regioselectivity:* ***242/243*** = 1:3.

R_f = 0.3 (Hexane:Ethyl acetate = 70:30). mp = 167-171 °C.

Representative Experimental Procedure: Prepared in accordance to the general procedure for the copper(I)-NHC-catalyzed allylic oxidation of cyclohexenes using **241** (0.060 g, 0.25 mmol) in 78%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.75-7.73 (m, 2H), 6.79-6.78 (m, 1H), 4.77 (qd, J = 13.9, 11.4, 4.7 Hz, 1H), 3.45 (dd, J = 16.0, 13.9 Hz, 1H), 3.32-3.25 (m, 1H), 2.63 (ddd, J = 16.0, 4.4, 1.6 Hz, 1H), 2.50-2.44 (m, 1H), 1.84 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.41 (e), 168.12 (e), 142.94 (o), 136.26 (e), 134.40 (o), 131.84 (e), 123.57 (o), 46.29 (o), 41.67 (e), 29.85 (e), 15.84 (o).

IR (Neat) 2924 (w), 1703 (vs), 1665 (vs), 1467 (w), 1371 (s), 1102 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{13}NO_3Na$ 278.0793, found 278.0796.

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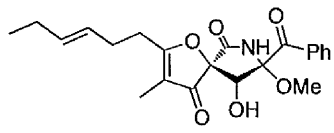
Chapter 3

Studies Towards The Total Synthesis of Cephalimysin A

3.1. Introduction

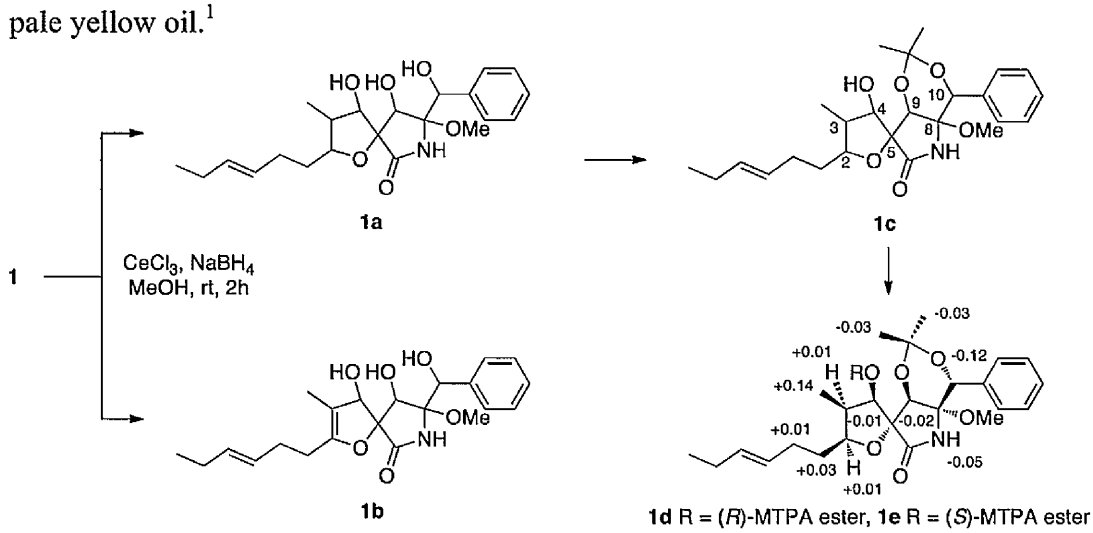
3.1.1. Isolation, Activity and Background

Cephalimysin A **1** was first isolated in 2007 by Yamada *et al.* from a strain of *Aspergillus fumigatus* OUPS-T106B-5, derived from the marine fish *Mugil cephalus*.[1] This agent **1** exhibits cytotoxicity against the murine P388 and human HL-60 leukemia cell line, with significant activity of IC_{50} 15.0 and 9.5 nM, respectively.



Cephalimysin A (1)

The strain **1** from *Mugil cephalus* fish was cultured at 27 °C for 6 weeks in a medium containing 1% soluble starch and 0.1% casein, buffered to pH 7.4, in 50% artificial seawater. The purification of cephalimysin A **1** was carried out by bioassay-directed fractionation, employing a stepwise combination of Sephadex LH-20, silica gel column chromatography and reverse phase HPLC to provide the natural product **1** as pale yellow oil.[1]



1d R = (*R*)-MTPA ester, **1e** R = (*S*)-MTPA ester

Scheme 3.1 *Determination of Absolute Stereochemistry of Cephalimysin A 1.*

The structural elucidation of **1** was based on detailed NMR studies (1D and 2D NMR), although the relative stereochemistry could not be determined using NOESY experiments. Cephalimysin A **1** was elaborated by the cerium(III) chloride mediated reduction to the triols **1a** and **1b**, and subsequent acetonide formation to afford exclusively **1c** (Scheme 3.1).[1] NOESY studies were performed on **1c**, which established the *anti/anti*-relationship between the C4-C5, H9 and 8-OMe, thus providing the desired relative stereochemistry. The absolute stereochemistry was identified *via* the modified Mosher's method, where **1c** was converted to the (*R*)- and (*S*)-MTPA esters **1d** and **1e**.[2] The ^{1}H-NMR chemical shift differences were compared and the absolute stereochemistry was assigned with the 2*S*, 3*S*, 4*R*, 5*R*, 8*S*, 9*R* and 10*R* configurations.

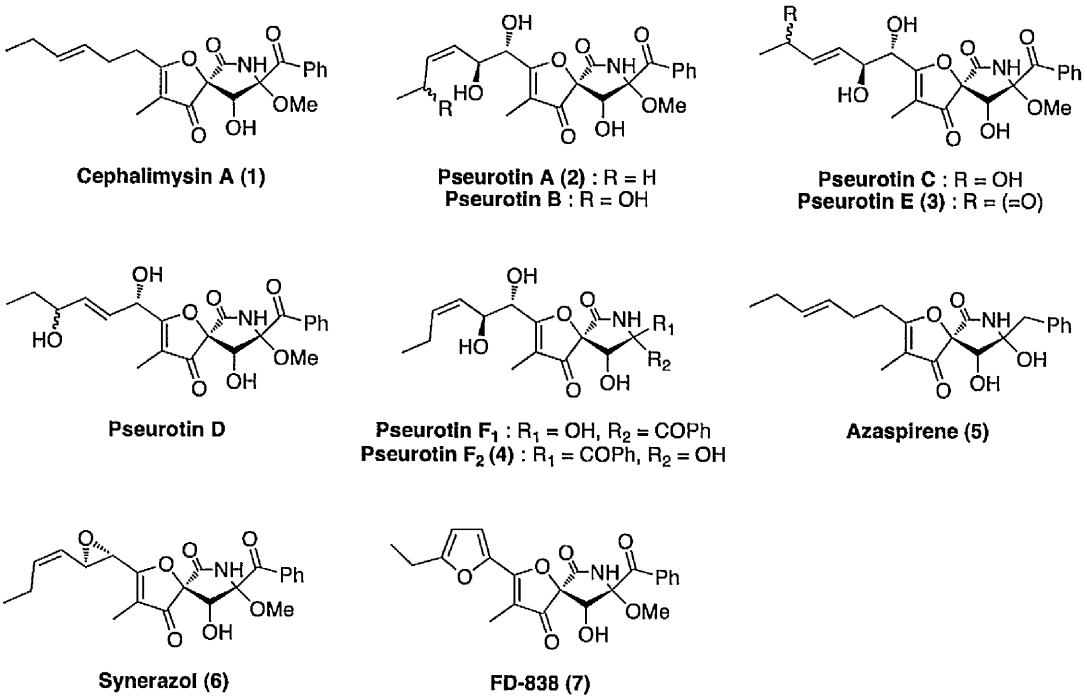
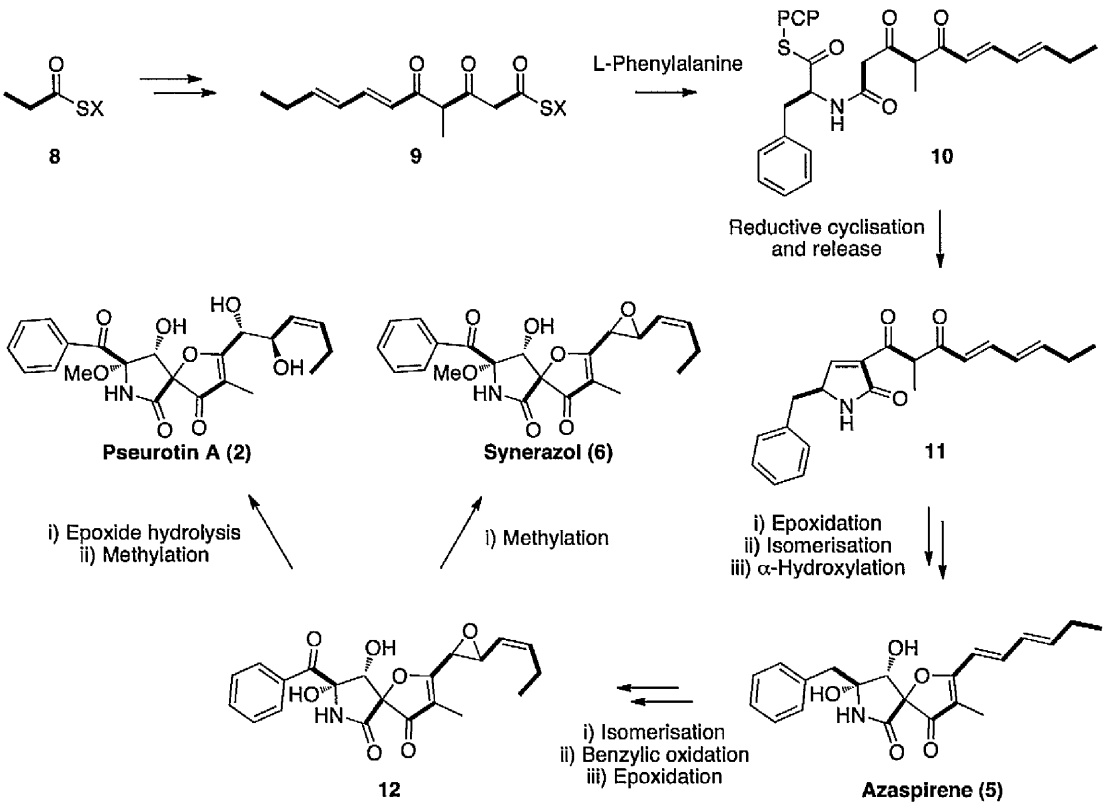


Figure 3.1 *1-Oxa-7-azaspiro[4.4]non-2-ene-4,6-dione Containing Natural Products.*

Cephalimysin A **1** contains a highly functionalised 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton, which is found in a plethora of other related natural products, as outlined in Figure 3.1.[3-8] The total synthesis of cephalimysin A **1** has not been forthcoming, but other members of this family have been prepared, including

pseurotin A **2**, E **3**, F_2 **4**, azaspirene **5**, synerazol **6** and FD-838 **7**.[4-8] Due to the novel, highly substituted and oxygenated core of these natural products, their total syntheses provide a significant challenge.

In 2007, Turner *et al.* identified a single hybrid polyketide synthase/non-ribosomal peptide synthetase (PKS/NRPS) gene required for the biosynthesis of pseurotin A **2** from the human pathogen *Aspergillus fumigatus*.[9] It was revealed that the presence of a PKS/NRPS gene, within a cluster of five genes, was involved in the secondary metabolism.



Scheme 3.2 *Proposed Biosynthesis of Pseurotin A 2 and Related Natural Products.*

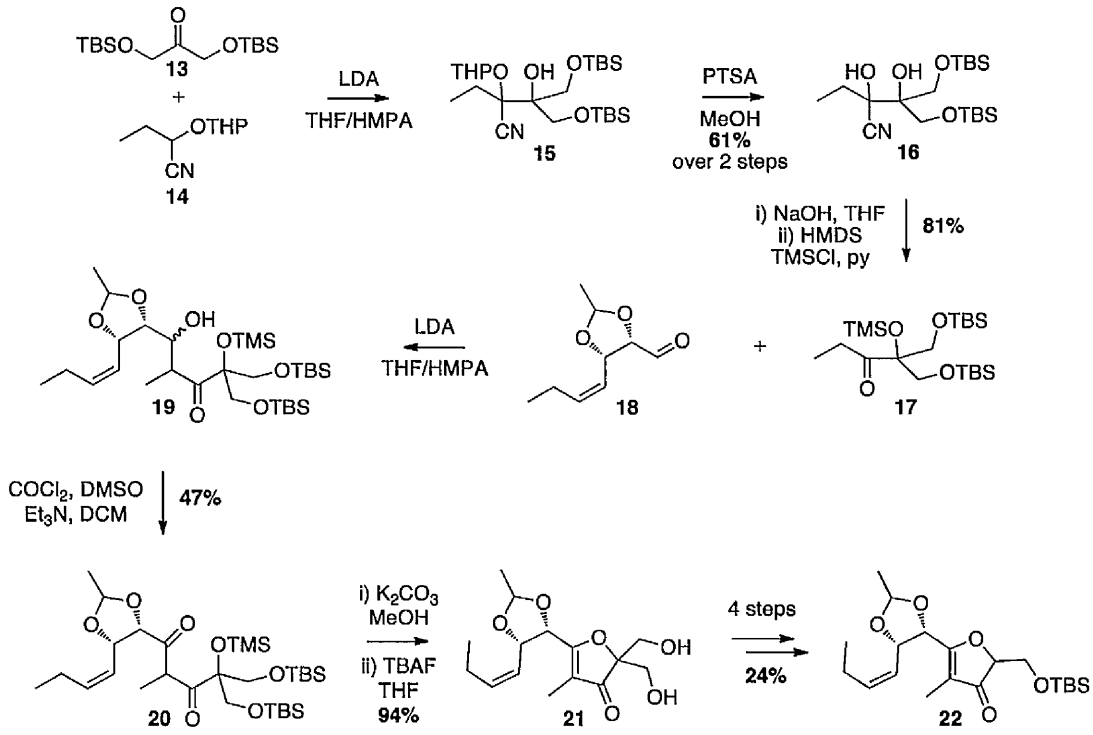
The pentaketide **9** was produced from the thioester **8** by five domain genes (KS: ketosynthase, AT: acyltransferase, DH: dehydratase, KR: ketoreductase and CMeT: C-methyltransferase) (Scheme 3.2).[9] The condensation of polyketide **9** and adenylated L-phenylalanine afforded the PKS-NRPS-bound intermediate **10**. The cyclisation and release of **10** provided the pyrrolidinone intermediate **11**. Through a

sequence of epoxidation, isomerisation and α-hydroxylation, by EAL85114 and EAL8511 (sequence similarities to hydrolase/dienelactone hydrolase and P450 monooxygenase, respectively), the successful conversion of **11** to azaspirene **5** was achieved. Additional alkene isomerisation/benzylic oxidation and epoxidation of azaspirene **5**, leads to the intermediate **12**. It was suggested that some of these steps could take place elsewhere in the genome as only one P450 is present in the gene cluster. Synerazol **6** would arise from the *O*-methylation of intermediate **12** by EAL85122 catalysis, and pseurotin A **2** from the epoxide hydrolysis of **12** by EAL85110 catalysis and EAL85122-catalysed *O*-methylation. This study identifies azaspirene **5** as the parent natural product, from which the other members of the family are prepared.

3.1.2. Syntheses of Other 1-Oxa-7-azaspiro[4.4]non-2-ene-4,6-dione Skeleton Natural Products

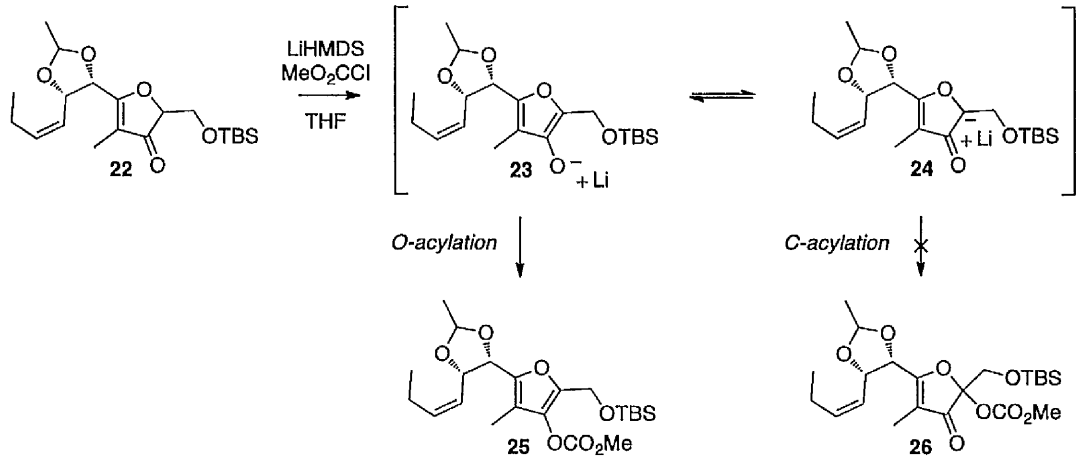
Pseurotin A **2**, first isolated in 1976 by Bloch and Tamm from a culture broth of *Pseudeurotium ovalis* (strain S2269/F) demonstrates a variety of biological activities, including chitin synthase inhibition, induction of cell differentiation and the inhibition of immunoglobulin E (IgE) production.[10] In 1990, Tamm *et al.* reported the synthesis of a furan-3(2*H*)-one core in an approach to pseurotin A **2** (Scheme 3.3).[11] The synthesis proceeded with the deprotonation of cyanohydrin **14** with LDA and reaction with silyl ketone **13**, which provided the alcohol **15**. The THP protecting group was removed selectively with PTSA in methanol to afford diol **16** in 61% yield over two steps. Ketone **17** was accessed through a retrocyanohydrin reaction with sodium hydroxide and subsequent silylation of the hydroxyl group, which proceeded in 81% yield. Condensation of ketone **17** with aldehyde **18** (previously prepared in 5 steps from D-glucose)[12] using LDA furnished

hydroxyketone **19**. This was immediately subjected to Swern oxidation to generate the diketone **20** in moderate yield. Treatment of **20** with acid afforded the cyclisation product, albeit with complete deprotection. This problem was solved by performing the cyclisation of **20** under basic conditions, followed by TBAF deprotection of the silyl groups to retain the cyclic acetal present and furnish the diol **21** in an excellent 94% yield. The diol **21** was converted into the key silyl ether **22** in 24% yield in four additional steps.[11]



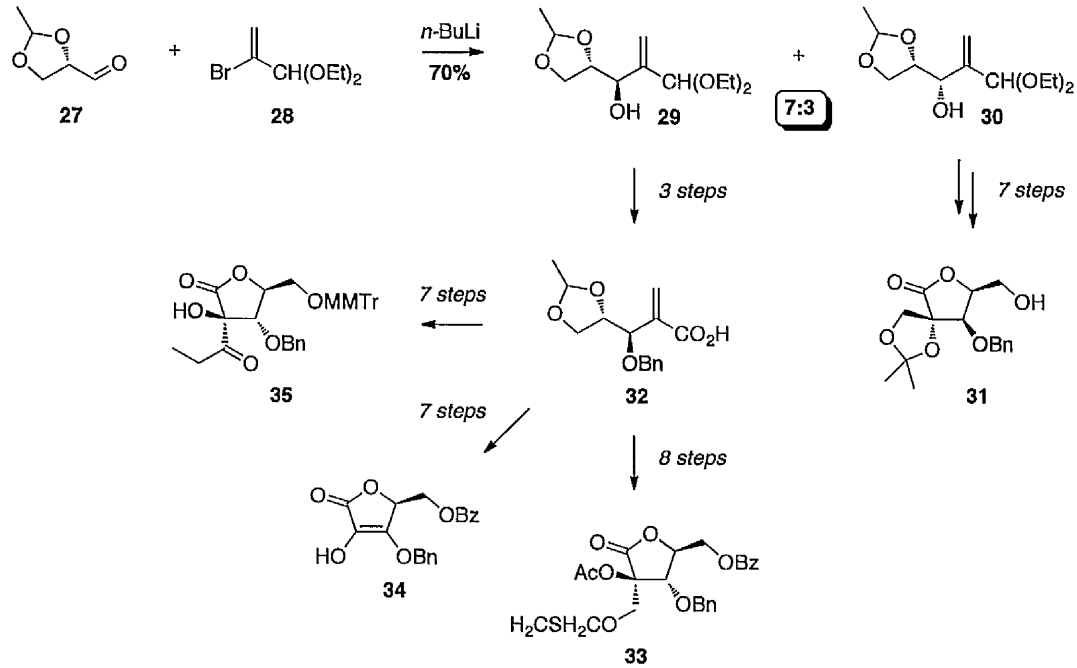
Scheme 3.3 *Synthesis of the Furan-3(2H)-one Core by Tamm et al.*

With the key silyl ether **22** in hand, introduction of a methoxycarbonyl group was attempted by LiHMDS deprotonation of **22** and treatment with methyl chloroformate (Scheme 3.4). Unfortunately, *O*-acylation occurred predominantly over the desired *C*-acylation and furan derivative **25** was obtained.[11] The *O*-alkylation is presumably the result of the formation of the highly stable enolate **23** due to the aromatic nature of the *pseudo*-furan, which disfavours *C*-acylation.



Scheme 3.4 *Failed Acylation Step of Furan-3(2H)-one Synthesis by Tamm et al.*

Tamm and Su provided an alternative route for the syntheses of the functionalised γ-lactone for pseurotin A **2** (Scheme 3.5).[13] Vinylbromide **28** was converted into the vinyl lithium by treatment with *n*-BuLi, and this was added to the aldehyde **27** to afford a 7:3 diastereomeric mixture of allylic alcohols **29/30** in 70% yield (Scheme 3.5). The minor diastereomer **30** was further functionalised in 7 steps to provide γ-lactone **31**, albeit possessing the opposite stereochemistry of pseurotin A **2**.[13]

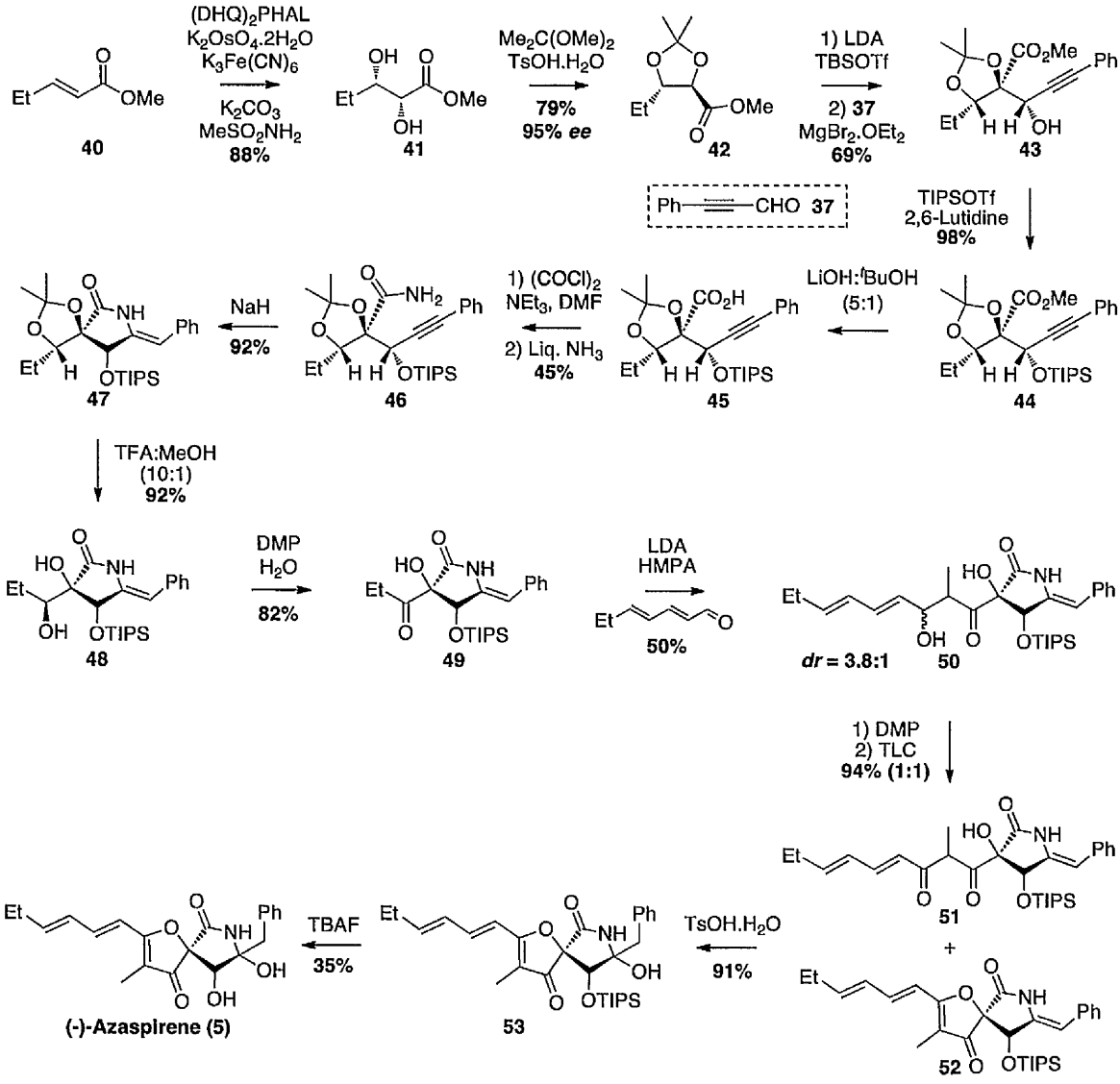


Scheme 3.5 *Synthesis of γ-Lactones by Tamm and Su.*

The major diastereomer **29** was transformed into a variety of highly substituted γ-lactones *via* carboxylic acid **32** (Scheme 3.5). For example, the synthesis of the thioester **33** was accomplished in 8 steps, whereas the enol lactone **34** was prepared in 7 steps from the carboxylic acid **32**. Alternatively, the γ-lactone **35**, which has the correct relative configuration of pseurotin A **2** was obtained in excellent overall yield *via* a 7 step sequence (10 total steps from aldehyde **27**).[13]

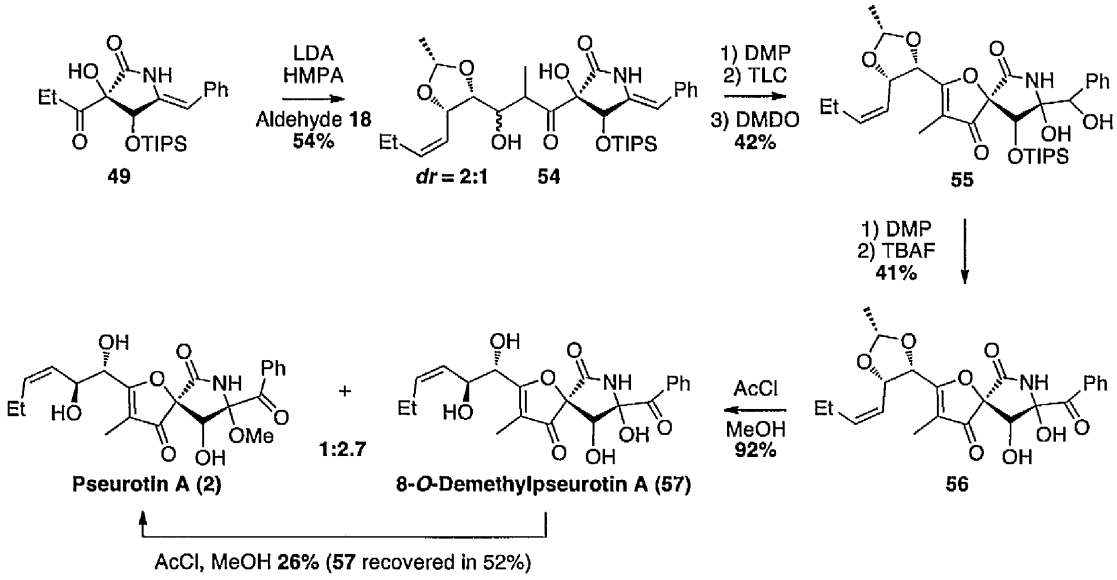
It was not until 2002 that Hayashi reported the first total synthesis of (−)-azaspirene **5**, which was the first synthesis of any member of this family.[6] (−)-Azaspirene **5** was isolated in 1990 from the fungus *Neosartorya sp*, and possessed inhibitory activity against angiogenesis-related diseases, for example, cancer and rheumatoid arthritis.[14]

The total synthesis of (−)-azaspirene **5** was accomplished as outlined in Scheme 3.6. Sharpless asymmetric dihydroxylation of methyl 2-pentenoate **40** provided diol **41** in 88% yield, which was converted to the acetal **42** for the Mukaiyama aldol reaction to afford the *syn*-aldol **43** in 69% yield (Scheme 3.6).[14] The alcohol **43** was transformed to the key intermediate **49** *via* a 7 step sequence. Aldol condensation of **49** with heptadienal generated **50** in 50% yield as a 3.8:1 mixture of diastereomers, which was inconsequential. The alcohol **50** was oxidised to the diketone **51**, which was partially converted into the bicycle **52** in 94% yield as a 1:1 mixture. When the mixture of diketone **51** and bicycle **52** was treated with catalytic acid, alcohol **53** was afforded as a single isomer in a convergent manner. Hayashi noted that the order of the last two steps was important as **52** underwent a proposed retro-aldol reaction in the presence of TBAF. Thus, the first total synthesis of (−)-azaspirene **5** was achieved with longest linear sequence of 16 steps.[14]



Scheme 3.6 *Total Synthesis of (-)-Azaspirene 5 by Hayashi et al.*

The landmark synthesis of (−)-azaspirene **5** by Hayashi *et al.* inspired the total synthesis of the other members of the family. In 2003, Hayashi described the first total synthesis of pseurotin A **2**, which had proven to be a particularly challenging target. Hayashi modified the strategy utilised in the total synthesis of (−)-azaspirene **5** (Scheme 3.7).[14] Aldol condensation of the methyl ketone **49** (11 steps from methyl 2-pentenoate **40**) with the aldehyde **18**[12] furnished a 2:1 diastereomeric mixture of aldol products **54** in 54% yield.[4a]



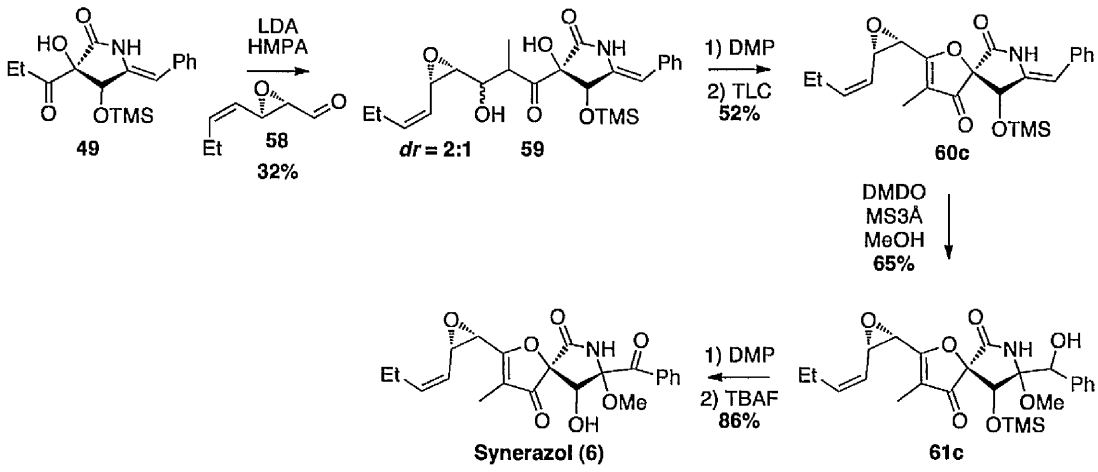
Scheme 3.7 *Total Synthesis of Pseurotin A 2 by Hayashi et al.*

Fortunately, this diastereomeric mixture was inconsequential as the epimeric alcohols **54** were oxidised to the corresponding ketone (Scheme 3.7). DMDO epoxidation/epoxide opening afforded the diol **55** in 42% yield. Further oxidation of the alcohol **55** to the ketone and deprotection provided the diol **56** in 41% yield. The synthesis was completed by the exposure of **56** to methanol pre-treated with acetyl chloride to provide pseurotin A **2** and 8-*O*-demethylpseurotin A **57** in 92% overall yield. Interestingly, 8-*O*-demethylpseurotin A **57** is a natural product, which was isolated with pseurotin A **2** as a 1:2.7 mixture.[16] 8-*O*-Demethylpseurotin A **57** can be converted to pseurotin A **2** by resubmitting it to the acetyl chloride/methanol conditions, albeit as a similar mixture. This completed the total synthesis of pseurotin A in 18 longest linear steps.[4a]

With a reliable strategy developed in the total syntheses of (−)-azaspirene **5** and pseurotin A **2**, Hayashi targeted another member of the 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione family, namely the total synthesis of synerazol **6**, which was isolated by Ando *et al* in 1991 from the cultured broth of *Aspergillus fumigatus* SANK 10588.[7] Synerazol **6** has remarkable biological activity against

Candida albicans and other fungi, and possesses synergistic antibiotic activity with azole-type antifungal agents.[17]

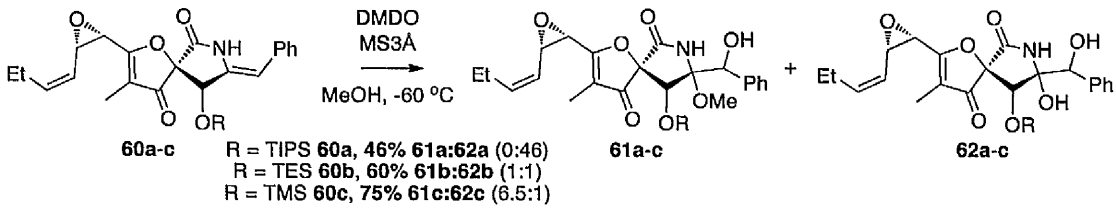
The total synthesis of synerazol **6** proceeded in a similar fashion to pseurotin A using the common building block **49** (Scheme 3.8).[7] The aldehyde **58** was prepared from D-tartaric acid diethyl ester in 9 steps,[18] and used in the aldol condensation with ketone **49** to afford a 2:1 diastereomeric mixture of aldol products **59** in 32% yield.[7] As in the synthesis of pseurotin A, the selectivity of **59** was irrelevant because the subsequent oxidation reaction provided the bicycle **60c** as single stereoisomer in 52% yield over the two steps.



Scheme 3.8 *Total Synthesis of Synerazol 6 by Hayashi et al.*

In the previous synthesis of pseurotin A **2**, the benzylidene moiety of **54** was epoxidised and ring-opened to access the diol functionality, with concomitant oxidation to provide the ketone **56** (Scheme 3.7).[4a] This approach was utilised in the first generation synthesis, although the efficiency of the tertiary alcohol methylation was poor (10% yield). Thus, an alternative plan was devised, in which it was envisaged that the epoxidation of the benzylidene moiety **60a-c** with DMDO in the presence of methanol would provide the alcohol **61a-c** (Scheme 3.9).[7] The examination of the silyl ether **60a-c** provided insight into the feasibility of this transformation, in which the TMS-protected **60c** in the presence of 3Å MS (to

scavenge water), afforded the methyl ether **61c** in 75% yield as 6.5:1 mixture of **61c** and the diol **62c**.



Scheme 3.9 *Epoxidation Optimisation in the Total Synthesis of Synerazol 6.*

The total synthesis was then completed by the oxidation and deprotection of the secondary alcohol **61c**, to furnish synerazol **6** in 86% yield over the two steps (Scheme 3.8). Hence, the first total synthesis of synerazol **6** was achieved with a longest linear sequence of 19 steps or 8 steps from the known ketone **49**.[7]

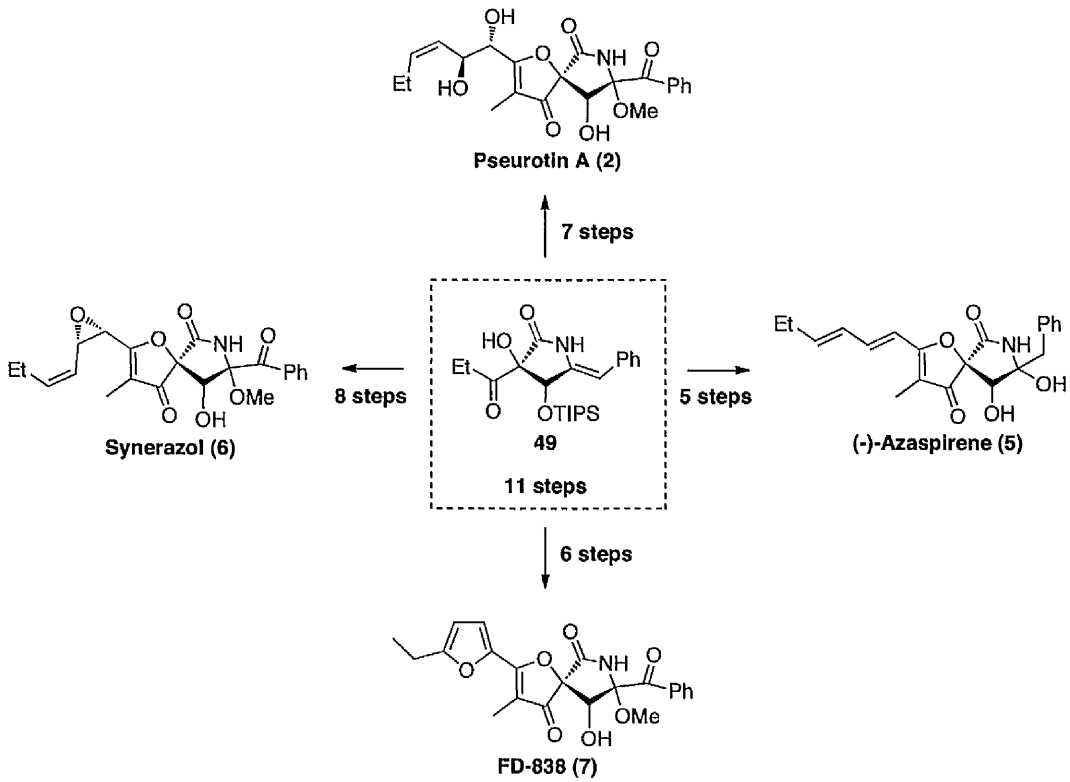
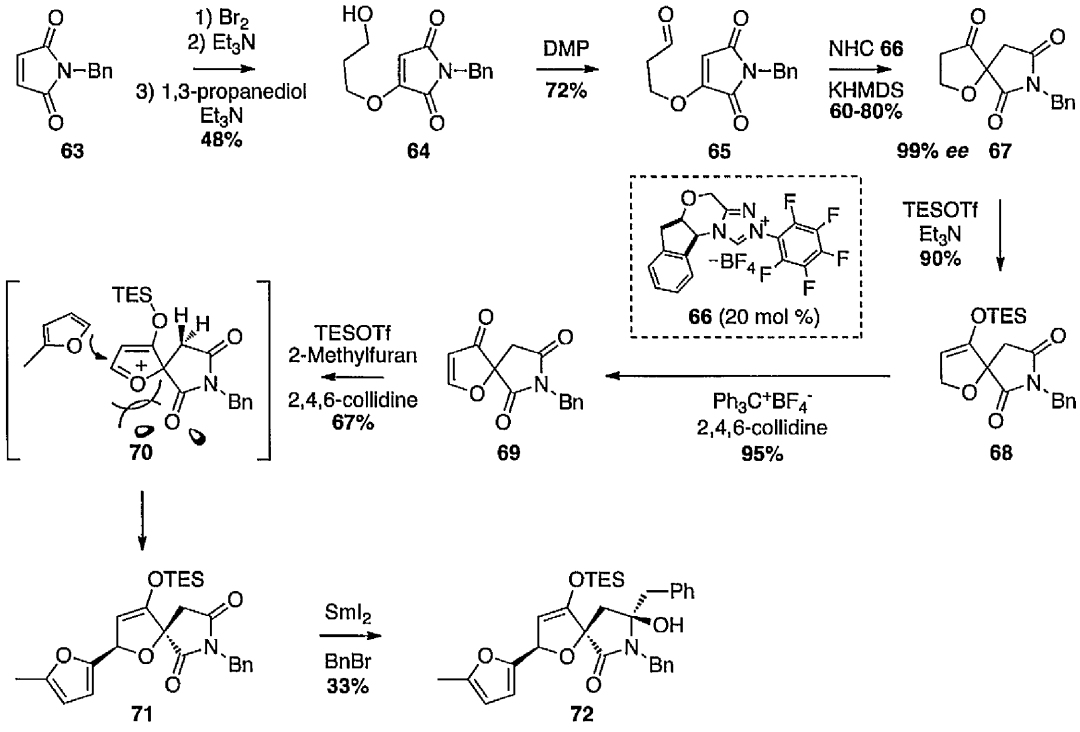


Figure 3.2 *Highly Divergent Syntheses of (-)-Azaspirene 5, Pseurotin A 2, Synerazol 6 and FD-838 7 from 1.*

Hayashi also illustrated a highly divergent synthetic strategy for the synthesis of the 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione family members (Fig. 3.2).[4a,6,7] In

addition to (-)-azaspirene **5**, pseurotin A **2** and synerazol **6**, the furan-containing derivative FD-838 **7** was also prepared. FD-838 **7** was isolated from *A. fumigatus fresenius* FD-838 by Mizoue *et al* in 1985[8a] and demonstrated both antibiotic and anti-cancer activity. It was prepared using a 17 step synthesis (6 steps from **49**).[8c]

In 2008, Rovis and Orellana reported the synthesis of the core of FD-838 **7**, utilising a catalytic asymmetric Stetter reaction (Scheme 3.10).[19] *N*-Benzyl maleimide **63** was converted into the alcohol **64** through a dibromination, elimination and addition-elimination sequence in 48% overall yield. Oxidation of the alcohol **64** afforded the necessary aldehyde **65** for the aforementioned key catalytic asymmetric Stetter reaction.[20] Treatment of **65** with 20 mol % of chiral triazolium salt **66** and KHMDS furnished the desired spirocycle **67** in 60-80% yield, and with excellent enantioselectivity (99% *ee*).[19]



Scheme 3.10 *Synthesis of the Core of FD-838 by Rovis et al.*

Conversion of **67** into the furanone **69** involved formation of the silyl enol ether **68**, and subsequent oxidation *via* a hydride abstraction using the trityl cation

(Scheme 3.10)..[21] The pendant furan was installed by the reaction of furanone **69** with a strong lewis acid and methylfuran to afford **71** in 67% yield. The transformation is proposed to proceed *via* the intermediate **70**, where the resonance-stabilised oxocarbenium ion is trapped by the furan, followed by rearomatisation to provide **71**. Interestingly, the solvent is critical since the reaction fails in dichloromethane and nitromethane, but is successful in acetonitrile, which is thought to stabilise the oxocarbenium ion by the formation of a nitrilium ion.[22] The synthesis of the core was completed by the regioselective Barbier-type alkylation of succinimide **71** with samarium diiodide and benzyl bromide, to generate the hemiaminal **72** in an unoptimised 33% yield.[19,23]

The total syntheses of the 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione natural products has prompted the preparation of analogues.[3] Figure 3.3 outlines some of the analogues reported, which are based on the fermentation and precursor-directed biosynthesis of pseurotin A **2**. The chemical modifications vary the side chain **73a-f**, oxygen/nitrogen capping **74a-b**, tetraol **75,** and fluorination of the aryl-ring **76a-b**.[24a-e]

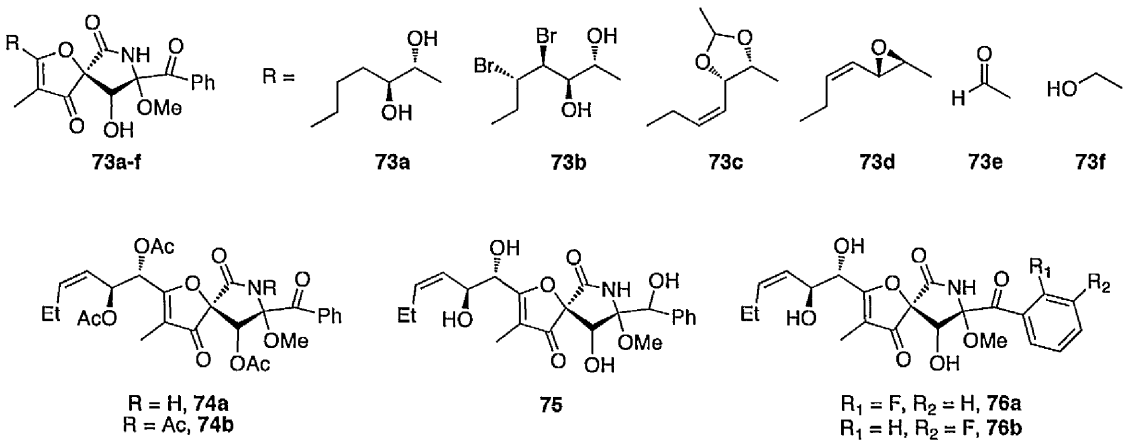
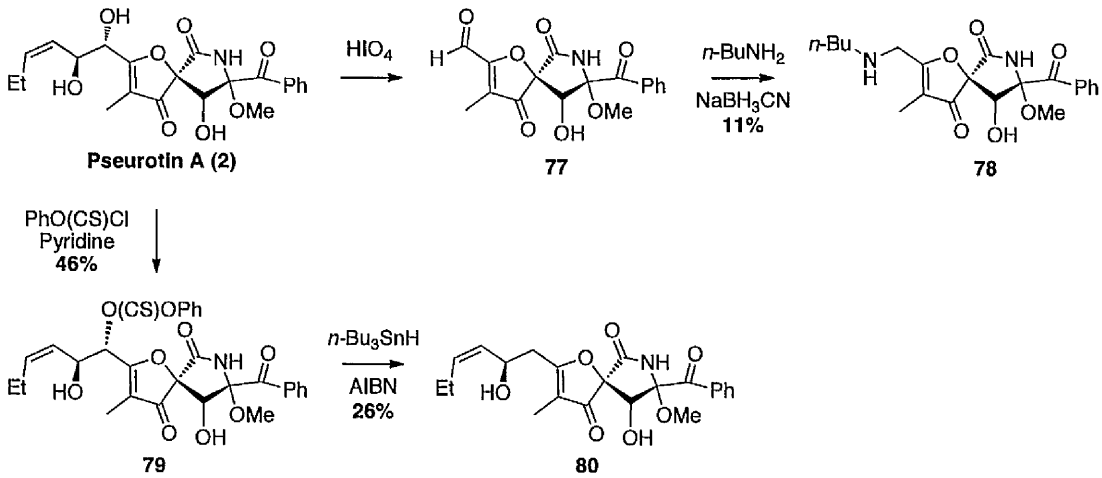


Figure 3.3 *Reported Pseurotin A Analogues 73-76.*

In 2009, Ishikawa reported the syntheses of pseurotin A analogues **78** and **80**, and their activity for the inhibition of immunoglobulin E (IgE) production (Scheme

3.11).[3] Pseurotin A **2** was subjected to oxidative cleavage to furnish the aldehyde **77**, which was subjected to reductive amination to afford the secondary amine **78** in poor yield.[3] Analogously, pseurotin A **2** was converted to the 10-*O*-thioacylated **79** in 46% yield, and reductive cleavage of the xanthate ester provided the 10-deoxypseurotin A **80** in 26% yield.[3]



Scheme 3.11 *Synthesis of Pseurotin A Analogues 78 and 80 by Ishikawa et al.*

Table 3.1 outlines the results of the biological studies in which pseurotin A **2** and the analogue **78** are modest inhibitors (3.6 and 3.1 μM, respectively) (Table 3.1, entries 1 and 3).[3] Synerazol **6** and 10-deoxypseurotin A **80** provided improved activities of 0.26 and 0.066 μM, respectively (entries 2 and 4). The results suggest that the 10-hydroxyl group of pseurotin A **2** is not required for activity (*cf.* **80**) and that the amino group in **78** presumably mimics the 11-hydroxyl group.[3]

Table 3.1 *IgE Inhibitory Activity and Specificity of Pseurotin Analogues 78 and 80.*

Entry	Compound	IgE IC_{50} (μM)	A IC_{50} (μM)	B IC_{50} (μM)	C	D IC_{50} (μM)
1	**2**	3.6	>10	>10	0%	>10
2	**6**	0.26	>10	>10	54%	3.1
3	**78**	3.1	>10	>10	2%	N/A
4	**80**	0.066	>10	4.4	0%	N/A
5	Prednisolone	0.0059	N/A	>10	84%	0.078

A = K562 cytotoxicity. B = B-cell viability. C = T-cell proliferation % inhibition at 10 μM. D = MLR.

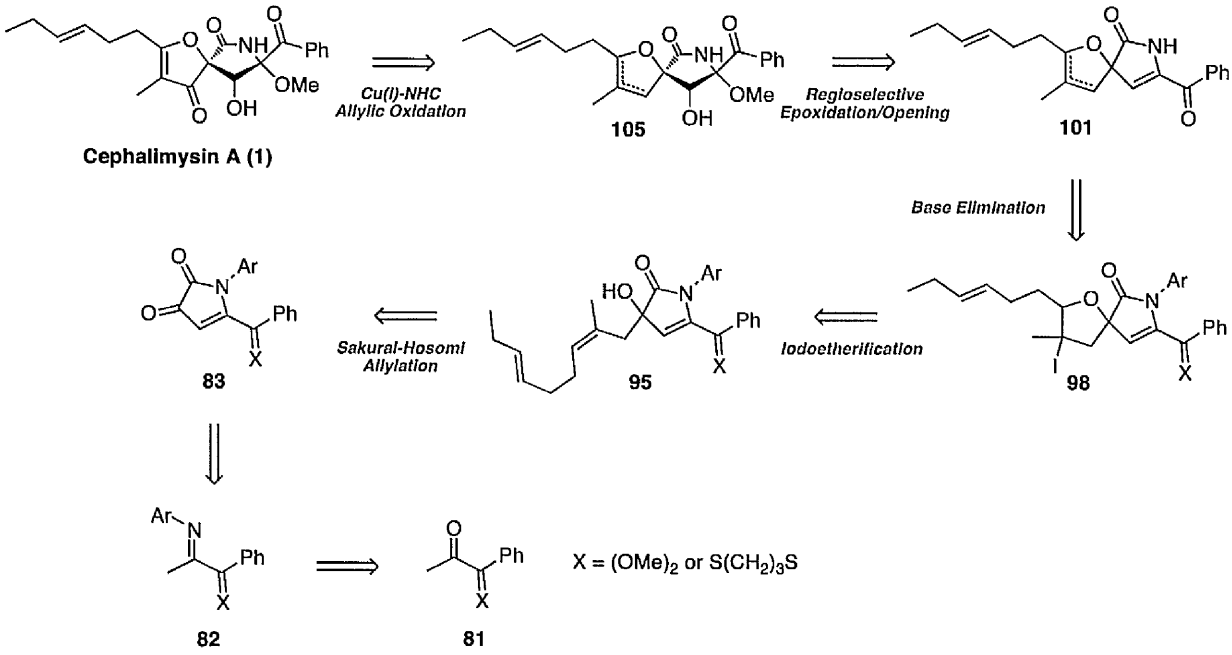
Pseurotin A **2**, synerazol **6** and the analogues **78** and **80** were further tested for specificity against K562 cytotoxicity, B-cell viability, T-cell proliferation and mixed-lymphocyte reaction (MLR).[3] Table 3.2 outlines the results with 10-deoxypseurotin A **80**, which indicate it is a potent and specific inhibitor of IgE production (Table 3.1, entry 4). Furthermore, synerazol **6** provides potent inhibition of T-cell proliferation and MLR, in addition to IgE production, suggesting that synerazol **6** has immunosuppressive activity (entry 2).[3]

3.2. Studies Towards the Total Synthesis of Cephalimysin A

3.2.1. Retrosynthetic Analysis

Cephalimysin A **1** is one of the members of the 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton containing natural product family, which has not been prepared.[1] The retrosynthetic analysis of cephalimysin A **1** is outlined in Scheme 3.12. The desired route would allow the application of a late stage copper(I)-NHC-catalysed allylic oxidation of intermediate **105** to afford the furanone.[25] The allylic oxidation of **105** is potentially problematic, owing to the presence of a secondary alcohol and acyclic alkene. We envisioned the copper(I)-NHC-catalysed allylic oxidation would permit the chemoselective oxidation.[25] The aldol product **105** would in turn be derived from the chemoselective nucleophilic epoxidation of the α, β-unsaturated ketone **101** in the presence of methanol to regioselectively open the epoxide *alpha* to nitrogen, in a similar manner to the route towards synerazol **6** (Scheme 3.12).[7] The cyclic alkene **101** could be prepared from the base-mediated elimination of iodide **98**, which would be prepared by the iodoetherification of the homoallylic alcohol **95** *via* a 5-*endo-trig* cyclisation. The homoallylic alcohol **95** would be installed using a regio- and chemoselective Hosomi-Sakurai allylation of dioxopyrroline **83**, providing the alkene side chain with the correct absolute and

relative stereochemistry. The key dioxopyrroline **83** would originate from the cyclisation of imine **82** with oxalyl chloride, which is prepared from the ketone **81** by imine condensation. This retrosynthetic route should facilitate the total synthesis of cephalimysin A **1** in a concise manner, as compared to previously reported 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton containing natural products.

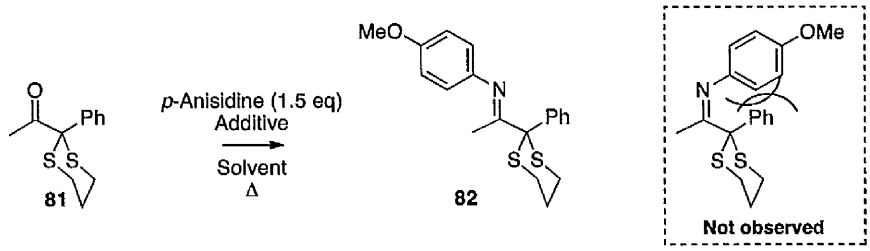


Scheme 3.12 *Retrosynthetic Analysis of the Total Synthesis of Cephalimysin A 1.*

3.2.2. Efforts Towards the Total Synthesis of Cephalimysin A

The synthesis was initiated with the preparation of imine **82** from the known ketone **81**[26] using *p*-anisidine under a variety of condensation conditions (Table 3.2). The *p*-anisidine group should facilitate the removal of the resulting *p*-methoxyphenyl (PMP) group under mild oxidative conditions.[27] The imine **82** was anticipated to adopt the favoured *E*-configuration due to steric interactions in the *Z*-isomer. Treatment of the ketone **81** with the anisidine in refluxing benzene afforded trace amounts of the desired imine **82** (Table 3.2, entry 1). Performing the condensation reaction under Dean-Stark conditions with acid or base provided similar results, with only trace quantities of **82** being observed (entries 2 and 3).[28]

Table 3.2 *Synthesis of Imine* ***82****.*

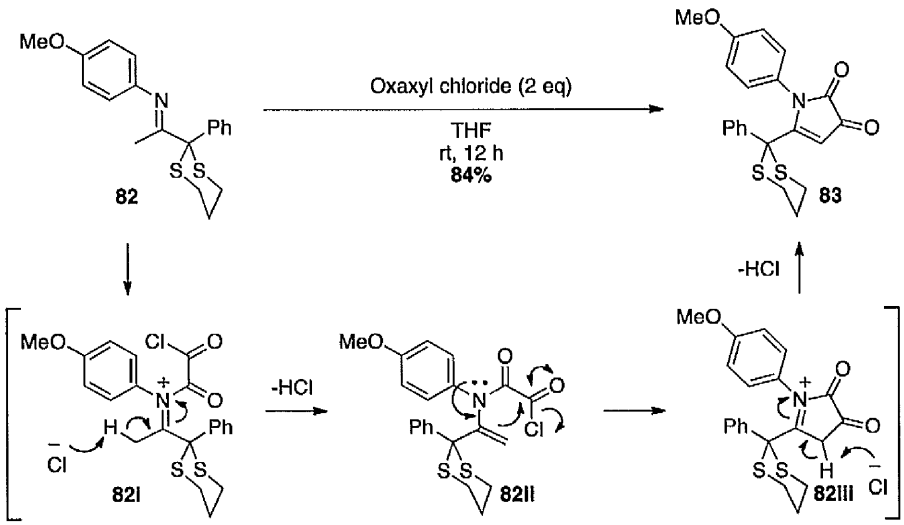


Entry	Additive	Solvent	Time (h)	Yield[a] (%)
1	-	PhH	48	Trace
2	PTSA (0.05 mol %)	PhMe	48	Trace
3	$NaHCO_3$ (2 eq)	PhMe	48	10
4	$TiCl_4$ (0.5 eq), Et_3N (2 eq)	DCM	24	20
5	$TiCl_4$ (1 eq)	PhMe	24	36
6	***$Ti(O\text{-}i\text{-}Pr)_4$ (1 eq)***	***PhMe***	***24***	***65***

[a]**Isolated yields.**

It is known that the imine condensation reactions of ketones are extremely difficult and inefficient, especially with a bulky group (dithiane) *alpha* to the ketone. Nevertheless, there were numerous successful variants that utilise a Lewis acidic titanium reagent to activate the carbonyl group for the addition.[29] Although the titanium tetrachloride mediated condensation only afforded the imine **82** in 20% yield, the analogous process in refluxing toluene gave an improved yield (Table 3.2, entries 4 and 5). The dissociation of hydrochloric acid from the titanium tetrachloride was envisioned to hydrolyse the imine **82** to the ketone **81**, thus an alternative titanium(IV) complex was investigated.[29] Treatment of the ketone **81** and *p*-anisidine with titanium isopropoxide in refluxing toluene furnished the imine **82** in 65% yield after 24 hours (entry 6). Interestingly, the imine **82** can be recrystallized in a range of organic solvents, providing a bench stable colourless solid.

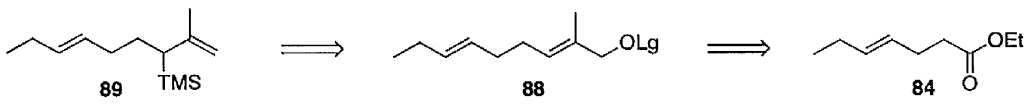
The dioxopyrroline **83** was prepared in 84% yield from the imine **82**, employing a modified procedure reported by Mohri using oxalyl chloride (Scheme 3.13).[30]



Scheme 3.13 *Synthesis of the Dioxopyrroline 83.*

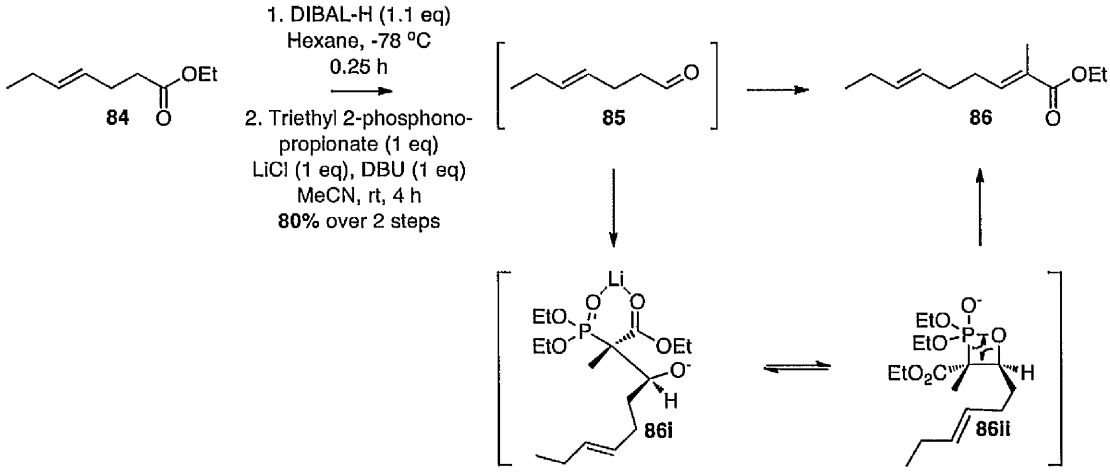
The proposed mechanism of the dioxopyrroline formation involves the nucleophilic addition of the nitrogen to the oxalyl chloride, to generate the iminium **82i** (Scheme 3.13). Tautomerisation of the iminium ion **82i** to the enamine **82ii**, followed by an intramolecular addition to the acid chloride affords the iminium intermediate **82iii**. Finally, tautomerisation of the intermediate **82iii** provides the dioxopyrroline **83**. Hence, the desired dioxopyrroline **83** was prepared on a multi-gram scale in two steps from the ketone **81** in 55% overall yield.

Scheme 3.14 outlines the strategy envisioned for the preparation of the requisite allylsilane **89**.[31] The allylsilane **89** would be prepared by an S_N2' reaction of **88** with a silyl cuprate. The substrate would be derived from the γ, δ-unsaturated ester **84**.



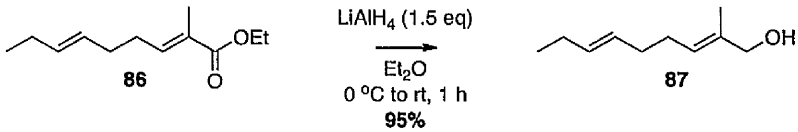
Scheme 3.14 *Retrosynthetic Analysis of Allylsilane 89.*

The synthesis of allylsilane **89** commenced with the reduction of the known γ, δ-unsaturated ester **84**[32] under modified DIBAL-H conditions to afford the aldehyde **85** (Scheme 3.15).[33] The crude aldehyde **85** was subjected to a Horner-Wadsworth-Emmons reaction, modified by Roush and Masamune, to provide the *α*, *β*-unsaturated ester **86** in 80% yield over the two steps, as predominantly the *E*-isomer.[34] The proposed mechanism leading to high *E*-selectivity is a result of the addition of the carbanion to the aldehyde **85** to furnish the *α*-hydroxyphosphonate **86i** (Scheme 3.15). The final elimination of intermediate **86ii** yields the *E*-alkene **86** in excellent stereoselectivity.[35]



Scheme 3.15 *Synthesis of the α, β-Unsaturated Ester 86.*

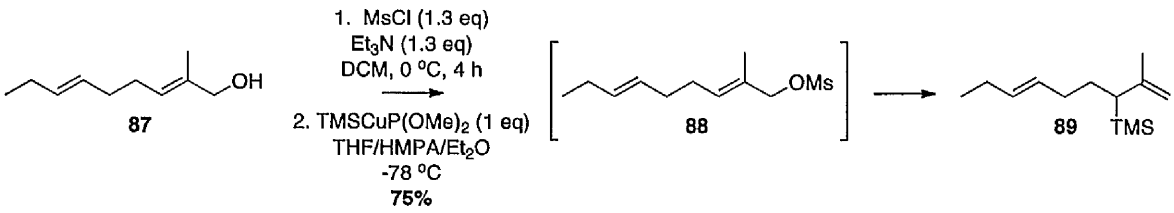
Reduction of the *α*, *β*-unsaturated ester **86** with excess $LiAlH_4$ was uneventful, affording the desired allylic alcohol **87** in 95% yield (Scheme 3.16).



Scheme 3.16 *The Synthesis of the Allylic Alcohol 87.*

Completion of the allylsilane synthesis was accomplished by conversion of the allylic alcohol **87** to the corresponding allylic mesylate **88**, which was used immediately (Scheme 3.17).[36] Treatment of $TMSCuP(OMe)_2$ (prepared from TMSLi

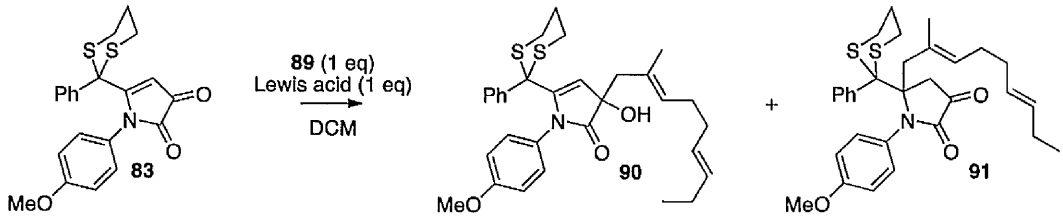
and $ICuP(OMe)_2$)[37] with the crude allylic mesylate **88** afforded the S_N2' displacement product **89** in 75% yield over two steps.[36]



Scheme 3.17 *Synthesis of the Allylsilane **89**.*

The Hosomi-Sakurai allylation of dioxopyrroline **83** was investigated with a variety of Lewis acids (Table 3.3). A solution of dioxopyrroline **83** and allylsilane **89** in dichloromethane at −78 °C was treated with a solution of boron trifluoride etherate to provide the desired homoallylic alcohol **90** in 10% yield, albeit with >19:1 regioselectivity (Table 3.3, entry 1).[36]

Table 3.3 *Regioselective Hosomi-Sakurai Allylation of Dioxopyrroline **83**.*

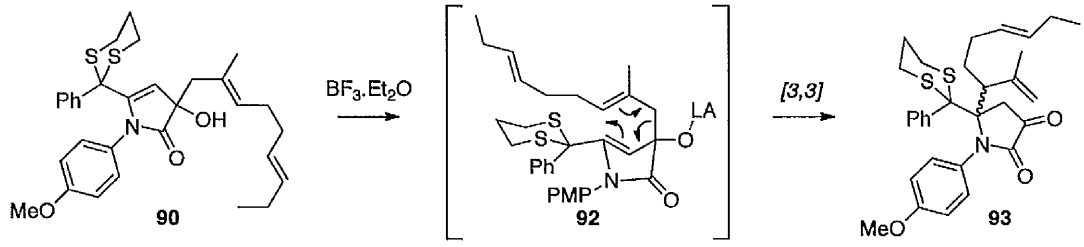


Entry	Lewis acid	T. (°C)	Time (h)	90:91	Yield[b] (%)
1	$BF_3.Et_2O$	-78	2	≥19:1	10
2[c]	$SnCl_4$	-78	12	≥19:1	10
3	***$SnCl_4$***	***0***	***2***	***≥19:1***	***71***
4	$TiCl_4$	0	2	≥19:1	48

[a]Determined by ^{1}H-NMR of crude mixture. [b]Isolated yields. [c]20% conversion.

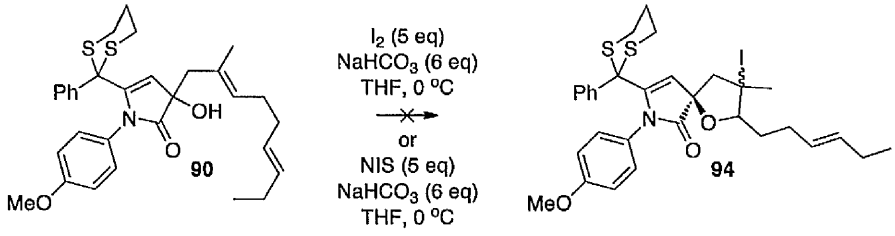
Presumably, the initial 1,2-addition product **90** is formed rather than the 1,4-addition product **91**, and after prolonged stirring under the reaction conditions, the intermediate **90** undergoes the [3,3]-sigmatropic oxy-Cope rearrangement to generate the product **93** (Scheme 3.18).[38] Unfortunately, the rearrangement is particularly facile under the boron trifluoride etherate conditions. Hence, a variety of Lewis acids

were examined to improve the efficiency of the Hosomi-Sakurai allylation, and eliminate formation of the oxy-Cope side product. Interestingly, tin(IV) chloride is unsuitable at -78 °C, albeit producing a single regioisomer after 12 hours (Table 3.3, entry 2). Gratifyingly, when the reaction was performed at 0 °C for 2 hours, the product **90** was obtained in 71% yield, with a minimal amount of oxy-Cope side product (entry 3). Finally, titanium(IV) chloride also provides **90** in a selective manner, albeit in modest yield (entry 4).



Scheme 3.18 *Proposed Oxy-Cope Sigmatropic Rearrangement of* ***90*** *with* $BF_3.Et_2O$.

The alkenyl alcohol **90** was then subjected directly to iodoetherification using standard conditions, namely, iodine and *N*-iodosuccinimide with sodium bicarbonate, which failed to afford any of the desired product **94** (Scheme 3.19).[39] We envisaged that the presence of the dithiane may interfere with the iodoetherification reaction, which prompted its conversion to the acetal **95**.[40]

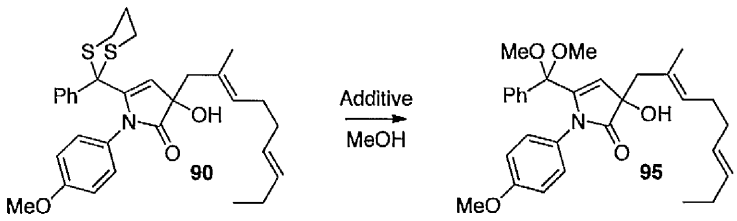


Scheme 3.19 *Direct Iodoetherification of Dithiane* ***90***.

Table 3.4 outlines the result of the study. Treatment of the dithiane **90** using the modified conditions, developed by Russell and Ochrymowycz (iodine/sodium bicarbonate in methanol), provided **95** in 23% yield after 6 hours (Table 3.4, entry 1).[41] Alternatively, the Corey and Erickson protocol, which utilises *N*-

bromosuccinimide/silver nitrate in methanol furnished **95** in 32% yield after 30 minutes (entry 2).[42] Nevertheless, each of these protocols can produce HI or HBr, which can lead to other side reactions (entries 1-2). Gratifyingly, the modified Stork and Zhao procedure, utilising [bis(trifluoroacetoxy)iodo]benzene [$PhI(TFA)_2$] in methanol with calcium carbonate, generated the desired product **95** in 75% yield after only 30 minutes (entry 3).[43]

Table 3.4 *Transacetalisation of Dithiane **90** to Acetal **95**.*

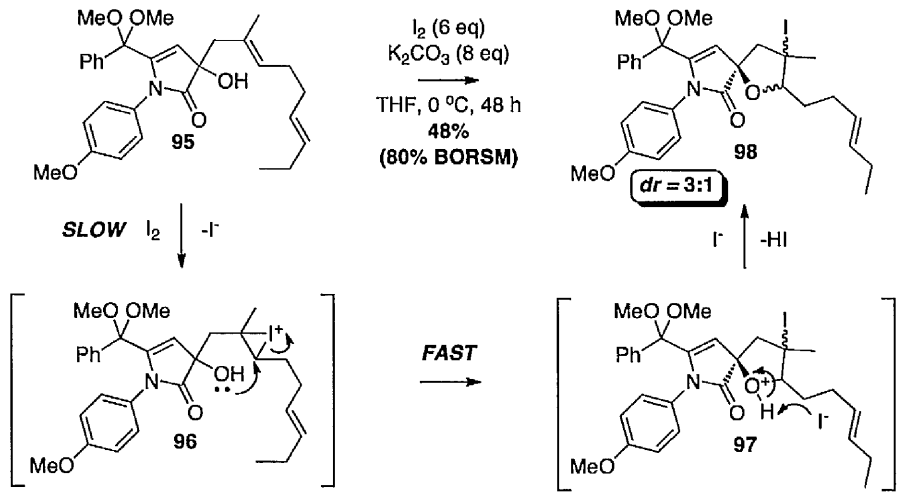


Entry	Additive[a]	T. (°C)	Time (h)	Conv. (%)	Yield[b] (%)
1	$I_2/NaHCO_3$	0	6	100	23
2	$NBS/AgNO_3$	0	0.5	100	32
3	***$PhI(TFA)_2/CaCO_3$***	***0***	***0.5***	***100***	***75***

[a]I_2 (2 eq)/$NaHCO_3$ (3 eq), NBS (2 eq)/$AgNO_3$ (2.2 eq), $PhI(TFA)_2$ (2 eq)/$CaCO_3$ (3 eq). [b]Isolated yields.

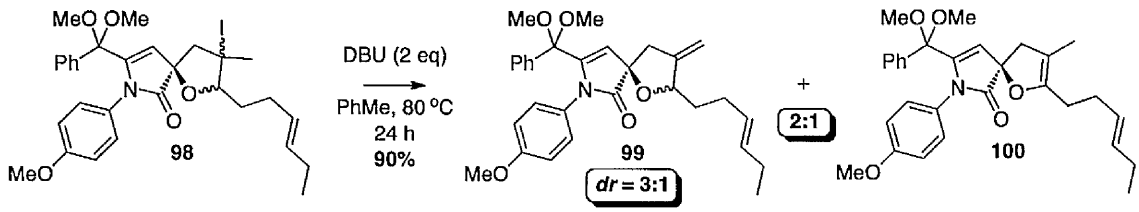
The acetal **95** was then resubjected to iodoetherification in the presence of iodine/potassium carbonate at 0 °C to generate a 3:1 diastereomeric mixture of the desired bicyclic product **98** in 48% yield after 48 hours (Scheme 3.20). Although the reaction is slow, the starting material **95** can be recovered in 40% yield to afford **98** in 80% yield based on recovered starting material (BORSM). The mixture of diastereomers is inconsequential, as the alkyl iodide stereocentre is destroyed in the subsequent elimination step. The low reactivity can be explained by the reversible addition of iodine to the desired double bond in **95**, forming the iodonium ion **96** (Scheme 3.20). Although, the 5-*endo-trig* cyclisation of the tertiary alcohol is fast due to the intramolecular opening of the highly reactive iodonium ion **96**, the rate-

determining step is the initial formation of the iodonium ion. Thus, the formation of the critical iodonium ion intermediate **96** could be improved by using a more electrophilic iodide species.[44]



Scheme 3.20 *Iodoetherification of Acetal 95.*

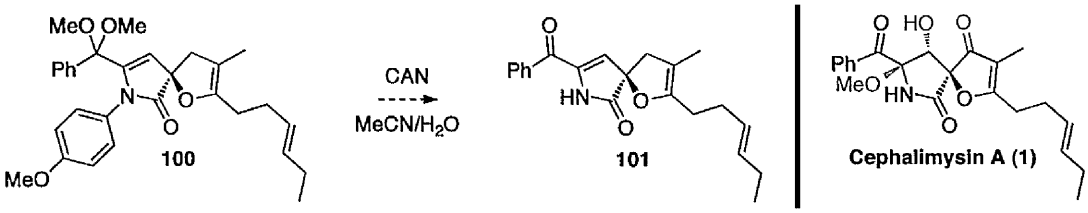
Iodide **98** was subjected to DBU-mediated elimination to afford a 2:1 regiomeric mixture of alkenes **99** and **100** in 90% yield (Scheme 3.21).[45] The *exo*-methylene **99** was obtained as a 3:1 diastereomeric mixture of products by ^{1}H-NMR. The desired enol ether **100** was observed as the minor regioisomer, presumably from the alkene isomerisation of **99**. The *exo*-methylene **99** is presumably the kinetic product, which under heating in toluene affords the more thermodynamically stable tetra-substituted enol ether **100**. Additional efforts are currently ongoing to optimise the conditions to isomerise the *exo*-methylene **99** to give the enol ether **100**.[46]



Scheme 3.21 *DBU Elimination of Iodide 98.*

3.2.3. Future Work Towards the Total Synthesis of Cephalimysin A

With access to the bicyclic enol ether **100** in a longest linear sequence of just six steps and 11 steps in total, the total synthesis of cephalimysin A **1** required a three-step sequence. It was envisaged that the acetal and *p*-methoxyphenyl (PMP) groups in **100** could be removed using cerium ammonium nitrate under aqueous conditions to expose the key enone moiety and the free amide of **101** (Scheme 3.22).[47] This would provide the complete carbon backbone of cephalimysin A **1**, with only the three oxygenated functionalities to be installed.

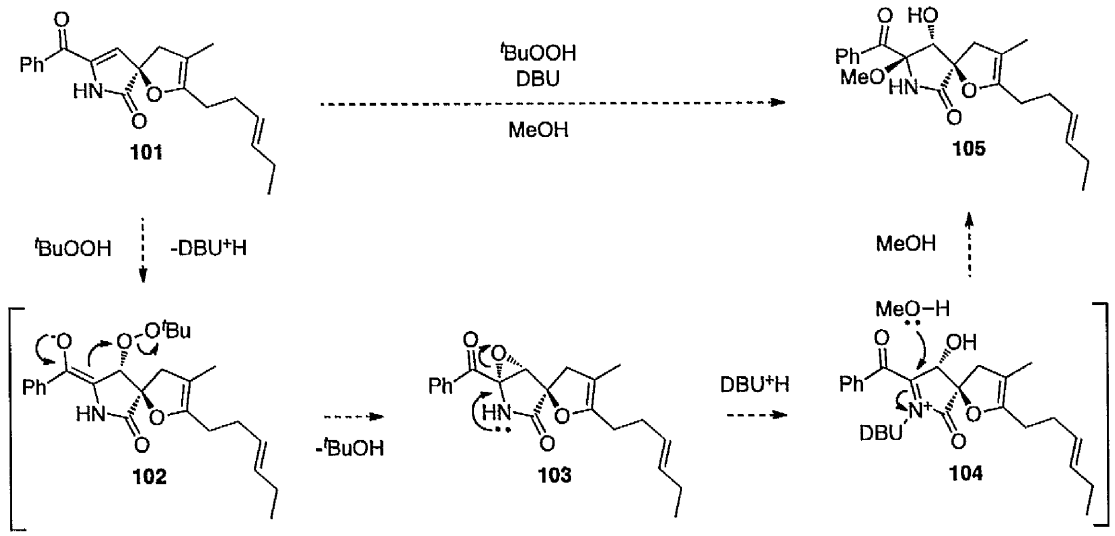


Scheme 3.22 *Deprotection of Acetal and PMP Groups in **100**.*

Treatment of enone **101** with *tert*-butyl hydroperoxide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is expected to facilitate a non-chelation nucleophilic epoxidation proceeding *via* the carbanion **102**, to afford the epoxy-ketone **103**, with the desired *anti*-stereochemistry (Scheme 3.23).[48] Intramolecular opening of the epoxide **103** by the adjacent nitrogen, which is activated by the protonated DBU, is expected to afford the iminium ion **104**. In the presence of methanol, the reactive iminium ion **104** is attacked on the opposite face to the neighbouring alcohol, to generate the desired *anti*/*anti* aldol product **105** in a single step.[49]

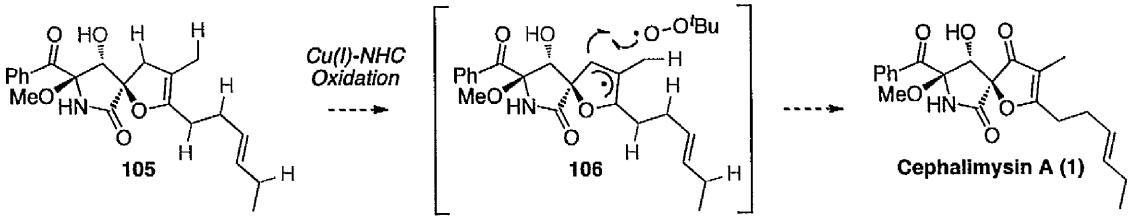
It was anticipated that the late-stage copper(I)-NHC-catalysed allylic oxidation of aldol product **105** would be highly chemo- and regioselective (Scheme 3.24).[25] Although there are potentially six sites of oxidation in **105**, the copper(I)-NHC-catalysed allylic oxidation should target only one.[25] It has already been demonstrated that acyclic allylic C-H and primary C-H bonds are resistant to allylic

oxidation, while the oxidation of secondary alcohols to ketones which utilise copper, normally require very harsh conditions, or strong oxidising agents (sodium hypochlorite).[50]



Scheme 3.23 *Epoxidation/Ring-Opening of Enone **101**.*

Using the copper(I)-NHC catalyst/*tert*-butyl hydroperoxide conditions, a chemo- and regioselective allylic hydrogen abstraction of the desired cyclic C-H bond of **105** will provide the allyl radical **106** (Scheme 3.24).[25] The recombination of the *tert*-butoxy radical and the allyl radical would be expected to occur at the least hindered side, based on previous experimental data, to furnish the desired furanone of cephalimysin A **1**.



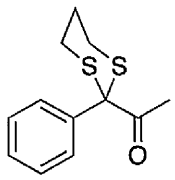
Scheme 3.24 *Late Stage Copper(I)-NHC-Catalysed Allylic Oxidation of **105**.*

3.3 Conclusions

In conclusion, it has been demonstrated that the essential bicycle **100** can be constructed in an expedient manner from the readily prepared dithiane **81** in a longest linear sequence of six steps, or 11 steps in total. The synthesis of **100** incorporates a regio- and chemoselective Hosomi-Sakurai allylation and an iodoetherification to generate the tetrahydrofuran ring system. The Hosomi-Sakurai allylation required the synthesis of the allyl silane **89** in 5 steps from the γ, δ-unsaturated ester **84**, utilising a copper-mediated S_N2' displacement reaction. Additional progress is currently being made on the synthesis of an enantiopure boronate for the enantioselective allylation *via* a chiral transfer procedure. Future work is aimed at the completion of the total synthesis of cephalimysin A **1** by the deprotection, epoxidation/ring-opening and copper(I)-NHC-catalysed allylic oxidation sequence outlined above. The successful application of the copper(I)-NHC-catalysed allylic oxidation on a highly functionalised intermediate, as the last step, would showcase the application of this methodology in natural product synthesis. Hence, the total synthesis of cephalimysin A **1** would be envisioned in a longest linear sequence of nine steps from the known dithiane **81**. Moreover, the enantioselective synthesis would provide a significant reduction in the number of steps compared to the earlier reported syntheses of 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione natural products (*cf.* Fig. 3.2).

3.4 Experimental

3.4.1. Experimental Procedures



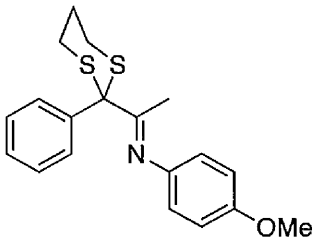
1-(2-Phenyl-1,3-dithian-2-yl)ethanone 81.[26]

Colour and state: Pale orange oil. R_f = 0.6 (Hexane:Ethyl acetate = 80:20).

Representative Experimental Procedure: Phenyl dithiane (19.63 g, 100 mmol) in tetrahydrofuran (500 mL) at -78 °C was treated with *n*-butyllithium (2.5 M in hexanes, 60 mL, 150 mmol) and stirred for 30 minutes. Acetaldehyde (8.42 mL, 150 mmol) was added to the red solution at -78 °C and slowly warmed to room temperature over 1 hour. The reaction was quenched with saturated aqueous ammonium chloride (200 mL), extracted three times with diethyl ether (200 mL) and washed with brine. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the alcohol. Dimethylsulfoxide (21.31 mL, 300 mmol) was stirred in dichloromethane (500 mL) at -78 °C and oxalyl chloride (12.69 mL, 150 mmol) was added dropwise. After 15 minutes, the crude alcohol was added dropwise to the reaction mixture and stirred at -78 °C for 1 hour. Triethylamine (69.69 mL, 500 mmol) was added dropwise to the reaction and slowly warmed to room temperature over 1 hour. The reaction was quenched with saturated aqueous ammonium chloride (200 mL), extracted three times with diethyl ether (200 mL) and washed with brine (300 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude ketone. Purification by flash chromatography (silica, 10% ethyl acetate/hexane) furnished 19.31 g (81%) of the ketone **81**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.42-7.39 (m, 2H), 7.37-7.34 (m, 1H), 3.15 (ddd, J = 14.4, 11.9, 2.6 Hz, 2H), 2.74 (ddd, J = 14.5, 5.0, 3.2 Hz, 2H), 2.15-2.07 (m, 1H), 2.11 (s, 3H), 1.93-1.84 (m, 1H).

IR (Neat) 2904 (w), 1705 (vs), 1488 (w), 1445 (m), 1423 (m), 1350 (m), 1164 (s) cm^{-1}.



(E)-4-methoxy-N-(1-(2-phenyl-1,3-dithian-2-yl) ethylidene)aniline 82.

Colour and state: Colorless solid. R_f = 0.5 (Hexane:Ethyl acetate = 80:20). mp = 84-86 °C.

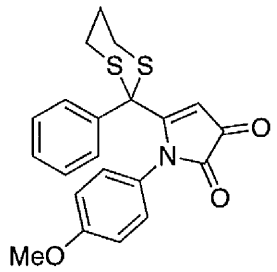
Representative Experimental Procedure: Ketone **81** (11.92 g, 50 mmol), *p*-anisidine (7.39 g, 60 mmol) and titanium isopropoxide (22.20 mL, 75 mmol) was stirred in toluene (50 mL) at 120 °C for 24 hours. The reaction mixture was cooled to room temperature and filtered through a plug of celite, washing with dichloromethane. Purification by flash chromatography (silica, 100% dichloromethane) furnished 11.16 g (65%) of the imine **82**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.81 (m, 2H), 7.43-7.40 (m, 2H), 7.34-7.31 (m, 1H), 6.87-6.85 (m, 2H), 6.75-6.72 (m, 2H), 3.79 (s, 3H), 3.14 (ddd, J = 14.1, 8.9, 3.0 Hz, 2H), 2.78 (ddd, J = 14.2, 7.9, 3.1 Hz, 2H), 2.13-2.06 (m, 1H), 2.03-1.96 (m, 1H), 1.70 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.37 (e), 156.13 (e), 143.93 (e), 139.46 (e), 128.94 (o), 128.25 (o), 128.13 (o), 120.49 (o), 114.28 (o), 64.57 (e), 55.53 (o), 28.54 (e), 25.03 (e), 17.27 (o).

IR (Neat) 2962 (w), 2935 (w), 2904 (w), 2888 (w), 2832 (w), 1649 (s), 1502 (vs), 1455 (m), 1357 (m), 1285 (m), 1240 (vs), 1200 (s), 1031 (s) 907 (s) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{19}H_{22}NOS_2$ 344.1143, found 344.1134.



1-(4-Methoxyphenyl)-5-(2-phenyl-1,3-dithian-2-yl)-1H-pyrrole-2,3-dione 83.

Colour and state: Orange solid. R_f = 0.3 (Hexane:Ethyl

acetate = 50:50). mp = 197-200 °C (decomposes).

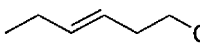
Representative Experimental Procedure: Imine **82** (6.87 g, 20 mmol) was stirred in tetrahydrofuran (100 mL) at room temperature and oxalyl chloride (3.38 mL, 40 mmol) was added dropwise. The reaction was stirred for 12 hours and concentrated *in vacuo*. Purification by flash chromatography (silica, 2% methanol/dichloromethane) furnished 6.68 g (84%) of the dioxopyrolline **83**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 6.51-6.50 (m, 2H), 6.35-6.33 (m, 2H), 3.72 (s, 3H), 3.13 (ddd, J = 14.3, 11.8, 2.8 Hz, 2H), 2.82 (dt, J = 14.5, 4.1 Hz, 2H), 2.16-2.13 (m, 1H), 1.97-1.88 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 184.20 (e), 174.88 (e), 160.32 (e), 159.41 (e), 137.71 (e), 131.69 (o), 129.69 (o), 129.13 (o), 126.82 (o), 125.75 (e), 113.41 (o), 104.51 (o), 55.43 (o), 54.76 (e), 29.03 (o), 23.44 (o).

IR (Neat) 3115 (w), 2912 (w), 2833 (w), 1752 (s), 1708 (vs), 1545 (s), 1509 (vs), 1298 (s), 1246 (vs), 1031 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{19}NO_3NaS_2$ 420.0704, found 420.0718.



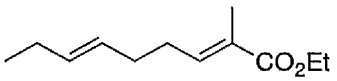
(*E*)-Ethyl hept-4-enoate 84.[32]

Colour and state: Colourless oil. R_f = 0.4 (Hexane:Ethyl acetate = 95:5).

Representative Experimental Procedure: 1-Penten-3-ol (10.27 mL, 100 mmol), propionic acid (3.70 mL, 5 mmol) and triethyl orthoacetate (91.66 mL, 400 mL) was stirred at 120 °C with a short-path distillation adapter (to remove ethanol formed) for 6 hours. The excess triethyl orthoacetate was distilled off at 160 °C, and the remaining reaction mixture was quenched with saturated aqueous sodium bicarbonate (200 mL). The mixture was extracted three times with diethyl ether (150 mL) and washed with brine (200 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 14.06 g (90%) of the ester **84**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53-5.48 (m, 1H), 5.42-5.36 (m, 1H), 4.13 (q, J = 14.3, 7.2 Hz, 2H), 2.37-2.28 (m, 4H), 2.02-1.96 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H).

IR (Neat) 2965 (w), 2935 (w), 1735 (vs), 1446 (w), 1372 (w), 1244 (w), 1163 (s), 966 (m) cm^{-1}.



(2*E*,6*E*)-Ethyl 2-methylnona-2,6-dienoate 86.

Colour and state: Colourless oil. R_f = 0.4 (Hexane:Ethyl acetate = 95:5).

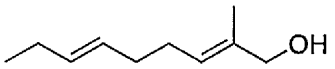
Representative Experimental Procedure: Ester **84** (3.91 g, 25 mmol) was stirred in hexane (250 mL) at -78 °C and DIBAL-H (1 M in hexanes, 37.50 mL, 37.50 mmol) was added, keeping the internal temperature at -78 °C. After 30 minutes, the reaction was quenched with methanol (2 mL) and warmed to room temperature. Saturated aqueous potassium sodium tartrate (500 mL) was added, stirred vigorously for 1 hour until homogeneous, extracted three times with diethyl ether (200 mL) and washed with brine (300 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* (100 mL) to yield the crude aldehyde, which was used immediately. Lithium chloride (11.13 g, 26.25 mmol) and triethyl 2-phosphonopropionate (5.36 mL, 25 mmol) was stirred in acetonitrile (200 mL) at 0 °C, to which DBU (3.74 mL, 25 mmol) was added dropwise. The reaction mixture was stirred for 15 minutes and the crude aldehyde was added *via* cannula to the reaction. The mixture was slowly warmed to room temperature over 1 hour, and was quenched with saturated aqueous ammonium chloride (200 mL), extracted three times with diethyl ether (150 mL) and washed with brine (200 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude ester. Purification by flash chromatography (silica, 5% ethyl acetate/hexane) furnished 3.93 g (80%) of the ester **86**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77-6.73 (m, 1H), 5.53-5.47 (m, 1H), 5.42-5.36 (m, 1H), 4.19 (q, J = 14.3, 7.2 Hz, 2H), 2.25-2.20 (m, 2H), 2.14-2.10 (m, 2H), 2.03-1.97 (m, 2H), 1.82 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.43 (e), 141.80 (o), 133.23 (o), 128.07 (e), 127.94 (o), 60.53 (e), 31.56 (e), 28.96 (e), 25.70 (e), 14.43 (o), 14.00 (o), 12.55 (o).

IR (Neat) 2963 (w), 1709 (vs), 1445 (w), 1367 (w), 1262 (s), 1107 (m), 966 (m) cm^{-1}.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{12}H_{24}O_2N$ 214.1523, found 214.1524.



(2*E*,6*E*)-2-Methylnona-2,6-dien-1-ol 87.

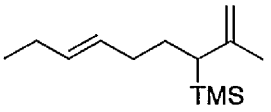
Colour and state: Colourless oil. R_f = 0.3 (Hexane:Ethyl acetate = 80:20).

Representative Experimental Procedure: Lithium aluminium hydride (1.14 g, 30 mmol) was added portion wise to diethyl ether (200 mL) at 0 °C and ester **86** (3.93 g, 20 mmol) was carefully added to the reaction slurry over 5 minutes. The stirring was maintained at 0 °C for 15 minutes and then slowly warmed to room temperature over 1 hour. The reaction was quenched with saturated aqueous potassium sodium tartrate (200 mL), stirred vigorously until homogeneous, extracted three times with diethyl ether (100 mL) and washed with brine (200 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude alcohol. Purification by flash chromatography (silica, 20% ethyl acetate/hexane) furnished 2.93 g (95%) of the alcohol **87**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50-5.37 (m, 3H), 4.00 (s, 2H), 2.12-1.97 (m, 7H), 1.67 (s, 3H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.00 (e), 132.54 (o), 128.66 (o), 125.91 (o), 68.98 (e), 32.50 (e), 27.88 (e), 25.69 (e), 14.02 (o), 13.81 (o).

IR (Neat) 3316 (br), 2962 (m), 2918 (m), 1438 (w), 1006 (s), 964 (vs) cm^{-1}.



(*E*)-Trimethyl(2-methylnona-1,6-dien-3-yl)silane 89.

Colour and state: Colourless oil. R_f = 0.7 (100% Hexane).

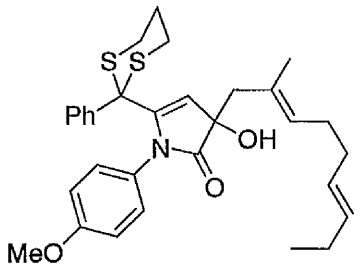
Representative Experimental Procedure: Copper iodide (2.00 g, 10.50 mmol) and trimethyl phosphite (1.24 mL, 10.50 mmol) were stirred in tetrahydrofuran (50 mL) with occasional heating using a heat gun until the solution went colourless. In a separate flask, hexamethylsilane (2.15 mL, 10.50 mmol) was stirred in tetrahydrofuran/HMPA (4:1, 50 mL) at -10 °C (ice/acetone bath) and methyllithium (1.6 M in diethyl ether, 6.56 mL, 10.50 mmol) was added dropwise, maintaining the internal temperature at -10 °C. The resulting solution was stirred for 15 minutes until it went dark red. The dark red solution was transferred *via* cannula to the $(MeO)_3PCuI$ solution at -78 °C and stirred for 15 minutes at -78 °C until it went dark brown. Alcohol **87** (1.54 g, 10 mmol) and triethylamine (1.81 mL, 13 mmol) was stirred in dichloromethane (50 mL) at -10 °C (ice/acetone bath) and methanesulfonyl chloride (1.01 mL, 13 mmol) was added slowly, resulting in a white slurry. This mixture was stirred vigorously for 30 minutes and quenched with water (50 mL). The blue/green mixture was extracted three times with diethyl ether (50 mL) and washed with brine (150 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude silane. Purification by flash chromatography (silica, 100% hexane) furnished 1.58 g (75%) of the silane **89**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46-5.41 (m, 1H), 5.39-5.33 (m, 1H), 4.60 (d, J = 101.1 Hz, 2H), 2.13-1.95 (m, 4H), 1.88-1.81 (m, 1H), 1.65 (s, 3H), 1.60-1.45 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H), -0.01 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.82 (e), 132.41 (o), 129.34 (o), 108.58 (e), 37.60 (o), 32.16 (e), 29.86 (e), 28.62 (e), 25.79 (e), 23.70 (o), 14.15 (o), -2.38 (o).

IR (Neat) 2961 (m), 2924 (m), 2853 (w), 1633 (w), 1439 (w), 1248 (m), 835 (s), 735 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calcd for $C_{13}H_{27}Si$ 211.1802, found 211.1807.



3-Hydroxy-1-(4-methoxyphenyl)-3-((2*E*,6*E*)-2-methylnona-2,6-dien-1-yl)-5-(2-phenyl-1,3-dithian-2-yl)-1*H*-pyrrol-2(3*H*)-one 90.

Colour and state: Pale yellow solid. R_f = 0.3 (Hexane:Ethyl acetate = 60:40). mp = 68-72 °C.

Representative Experimental Procedure: Dioxopyrolline **83** (1.99 g, 5 mmol) and silane **89** (1.05 g, 5 mmol) was stirred in dichloromethane (50 mL) at 0 °C to which, tin chloride (0.59 mL, 5 mmol) was added dropwise to the resulting solution. The reaction was stirred at 0 °C for 2 hours and quenched with saturated aqueous sodium bicarbonate (50 mL). The mixture was extracted three times with ethyl acetate (100 mL) and washed with brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude alcohol. Purification by flash chromatography (silica, 35% ethyl acetate/hexane) furnished 1.90 g (71%) of the alcohol **90**.

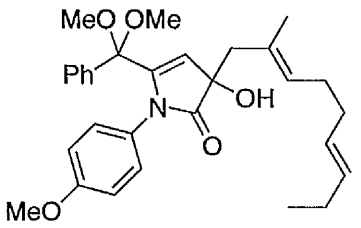
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.28-7.24 (m, 2H), 7.18-7.15 (m, 1H), 6.49-6.48 (m, 2H), 6.35-6.31 (m, 2H), 6.17 (s, 1H), 5.52-5.47 (m, 1H), 5.45-5.39 (m, 2H), 3.71 (s, 3H), 3.19-3.11 (m, 2H), 2.75-2.70 (m, 2H), 2.69-2.61 (m, 2H), 2.36 (bs, 1H), 2.18-2.13 (m, 2H), 2.10-2.06 (m, 3H), 2.04-1.98 (m, 2H), 1.94-1.84 (m, 1H), 1.82 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 181.29 (e), 158.91 (e), 146.05 (e), 139.35 (e), 132.80 (o), 131.51 (o), 130.59 (o), 129.82 (e), 128.74 (o), 128.59 (o), 128.55 (o), 127.69 (e), 127.23 (o), 115.23 (o), 113.20 (o), 55.39 (o), 54.41 (e), 48.22 (e), 32.61 (e), 29.16 (e), 28.65 (e), 25.73 (e), 24.08 (e), 18.52 (o), 14.05 (o).

IR (Neat) 3383 (br), 2958 (w), 2913 (w), 2838 (w), 1702 (s), 1609 (w), 1509 (vs),

1445 (w), 1244 (vs), 1033 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{31}H_{37}NO_3NaS_2$ 558.2113, found 558.2115.



5-(Dimethoxy(phenyl)methyl)-3-hydroxy-1-(4-methoxyphenyl)-3-((2*E*,6*E*)-2-methylnona-2,6-dien-1-yl)-1*H*-pyrrol-2(3*H*)-one 95.

Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Ethyl acetate = 60:40).

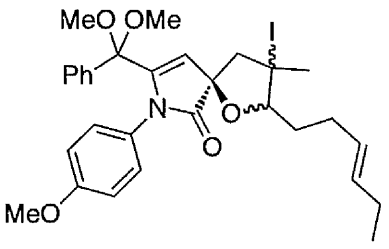
Representative Experimental Procedure: Dithiane **90** (0.54 g, 1 mmol) and calcium carbonate (0.30 g, 3 mmol) were stirred in dry methanol (10 mL) at 0 °C. [Bis(trifluoroacetoxy)iodo]benzene (0.86 g, 2 mmol) was added to the slurry in one portion and stirred at 0 °C for 30 minutes. The reaction was quenched with a 1:1 mixture of saturated aqueous sodium bicarbonate/sodium thiosulfate (10 mL) and stirred vigorously for 1 hour. The mixture was extracted three times with ethyl acetate (20 mL) and washed with brine (30 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude acetal. Purification by flash chromatography (silica, 30% ethyl acetate/hexane) furnished 0.66 g (75%) of the acetal **95**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.17 (m, 1H), 7.13-7.10 (m, 2H), 7.06-7.04 (m, 2H), 6.56-6.54 (m, 2H), 6.35 (bs, 2H), 5.96 (s, 1H), 5.52-5.47 (m, 1H), 5.44-5.39 (m, 1H), 5.35-5.33 (m, 1H), 3.74 (s, 3H), 3.08 (s, 6H), 2.60-2.54 (m, 2H), 2.12-2.05 (m, 6H), 2.01 (tt, J = 7.3 Hz, 2H), 1.77 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.77 (e), 159.10 (e), 145.78 (e), 137.45 (e), 132.76 (o), 130.44 (o), 130.05 (o), 129.58 (e), 128.68 (o), 128.36 (o), 127.76 (o), 127.50 (e), 127.33 (o), 113.56 (o), 112.00 (o), 98.82 (e), 77.08 (e), 55.52 (o), 49.05 (o), 48.90 (o), 48.00 (e), 32.61 (e), 28.60 (e), 25.73 (e), 18.61 (o), 14.05 (o).

IR (Neat) 3395 (br), 2960 (w), 1712 (m), 1512 (vs), 1451 (w), 1296 (w), 1248 (s), 1154 (m), 1064 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{30}H_{37}NO_5Na$ 514.2569, found 514.2571.



(*E*)-8-(Dimethoxy(phenyl)methyl)-2-(hex-3-en-1-yl)-3-iodo-7-(4-methoxyphenyl)-3-methyl-1-oxa-7-azaspiro[4.4]non-8-en-6-one 98.

Colour and state: Pale yellow oil. R_f = 0.3 (Hexane:Ethyl acetate = 90:10). *dr* = 3:1.

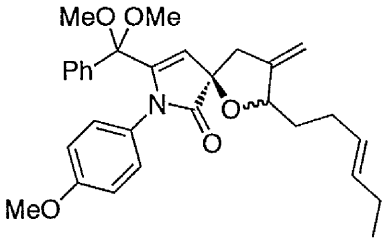
Representative Experimental Procedure: Acetal **95** (0.25 g, 0.5 mmol) and potassium carbonate (0.55 g, 4 mmol) was stirred in tetrahydrofuran (10 mL) at 0 °C. Iodine (0.76 g, 3 mmol) was added to the mixture in the dark and stirred at 0 °C for 48 hours. The reaction was quenched with a 1:1 mixture of saturated aqueous sodium bicarbonate/sodium thiosulfate (10 mL) and stirred vigorously for 1 hour. The mixture was extracted three times with ethyl acetate (20 mL) and washed with brine (30 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude iodide. Purification by flash chromatography (silica, 10% ethyl acetate/hexane) furnished 0.15 g (48%) of the iodide **98**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.18 (m, 1H), 7.16-7.11 (m, 2H), 7.09-7.05 (m, 2H), 6.54-6.53 (m, 2H), 6.41-6.34 (m, 2H), 5.87 (s, 1H), 5.57-5.51 (m, 1H), 5.49-5.43 (m, 1H), 3.74 (s, 3H), 3.16-3.07 (m, 2H), 3.10 (s, 3H), 3.07 (s, 3H), 2.34-2.28 (m, 1H), 2.19-1.99 (m, 6H), 1.96 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.39 (e), 159.09 (e), 146.78 (e), 137.20 (e), 132.83 (o), 130.22 (o), 128.42 (o), 127.84 (o), 127.56 (o), 127.48 (e), 127.27 (o), 127.16 (o), 113.49 (o), 111.27 (o), 90.17 (o), 81.88 (e), 55.64 (o), 54.69 (e), 48.93 (o), 40.75 (e), 30.24 (e), 29.91 (o), 28.44 (e), 25.74 (e), 14.06 (o).

IR (Neat) 2934 (w), 1715 (m), 1513 (vs), 1450 (w), 1298 (w), 1249 (s), 1147 (w), 1065 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{30}H_{36}NO_5NaI$ 640.1536, found 640.1558.



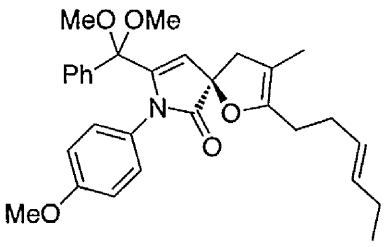
8-(Dimethoxy(phenyl)methyl)-2-((*E*)-hex-3-en-1-yl)-7-(4-methoxyphenyl)-3-methylene-1-oxa-7-azaspiro[4.4]non-8-en-6-one 99.

Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Ethyl acetate = 80:20). **99**:**100** = 3:1.

Representative Experimental Procedure: Iodide **98** (0.06 g, 0.10 mmol) was dissolved in toluene (1 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.02 mL, 0.20 mmol) was added. The reaction was stirred at 80 °C for 24 hours, cooled to room temperature and quenched with water (5 mL). The mixture was extracted three times with ethyl acetate (10 mL) and washed with brine (15 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography (silica, 15% ethyl acetate/hexane) furnished 0.04 g (90%) of the alkenes **99/100**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.21-7.18 (m, 1H), 7.14-7.11 (m, 2H), 6.54-6.52 (m, 2H), 6.42-6.35 (m, 2H), 5.87 (s, 1H), 5.08 (d, J = 2.2 Hz, 1H), 4.96 (d, J = 2.2 Hz, 1H), 3.73 (s, 3H), 3.10-3.09 (m, 6H), 2.93 (d, A of AB, J_{AB} = 15.7 Hz, 1H), 2.85 (d, B of AB, J_{AB} = 15.6 Hz, 1H), 2.35 (t, J = 7.6 Hz, 1H), 2.24-2.16 (m, 2H), 2.07-1.96 (m, 2H), 1.85-1.77 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H).

HRMS (ESI, $[M+Na]^+$) calcd for $C_{30}H_{35}NO_5Na$ 512.2413, found 512.2409.



(*E*)-8-(dimethoxy(phenyl)methyl)-2-(hex-3-en-1-yl)-7-(4-methoxyphenyl)-3-methyl-1-oxa-7-azaspiro[4.4]nona-2,8-dien-6-one 100.

Colour and state: Pale yellow oil. R_f = 0.4 (Hexane:Ethyl acetate = 80:20).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.18 (m, 1H), 7.16-7.11 (m, 2H), 7.09-7.05 (m, 2H), 6.54-6.53 (m, 2H), 6.41-6.34 (m, 2H), 5.87 (s, 1H), 5.57-5.51 (m, 1H), 5.49-5.43 (m, 1H), 4.65 (d, J = 9.7 Hz, 1H), 3.84-3.77 (m, 2H), 3.74 (s, 3H), 3.10 (s, 3H), 3.07 (s, 3H), 2.34-2.28 (m, 2H), 2.19-1.99 (m, 4H), 1.96 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H).

HRMS (ESI, $[M+Na]^+$) calcd for $C_{30}H_{35}NO_5Na$ 512.2413, found 512.2409.

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